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Original Articles

HYPERSENSITIVENESS OF THE MUCOUS MEMBRANE

IV. The Effect of Local Reactions Elicited by Specific and Nonspecific Excitants Upon the Ophthalmic Mucous Membrane in Allergic and Nonallergic Individuals

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IT HAS been shown by Bowman and Walzer[1] that whealing of the skin produced by specific and nonspecific excitants results in an alteration in the reactivity of the wheal sites to testing performed after an interval of a week. Histamine wheals produced a state of diminished permeability when the sites were retested with histamine in 79 per cent of cases. The sites were not refractory, however, when retested with a specific antigen such as ragweed. Where the original wheal was induced with the specific excitant, ragweed, subsequent retesting with ragweed or histamine showed increased permeability instead of refractoriness in 77 per cent and 90 per cent of cases respectively. In all instances, however, the erythema surrounding the wheals was diminished on restimulation of the tested sites. The erythematous response appeared to be decreased to the least extent in those experiments in which the histamine wheal sites were restimulated with ragweed.

The purpose of the present study was to ascertain what effects initial specific and nonspecific reactions in the ocular conjunctiva would have on responses to subsequent restimulation with specific and nonspecific excitants. A solution of histamine phosphate (1:1000 or 1:3000) was used as the nonspecific excitant; and a solution of ragweed pollen (0.1 mg. N per c.c.) was usually used as the specific excitant.

The subjects selected for study presented no acute nasal symptoms, ocular congestion, or inequality in conjunctival vascularity. All tests were performed outside of pollinating seasons. Pollen-sensitive patients were used for the studies with specific excitants. The nonallergic group consisted mainly of patients with refractive errors; others had cataract, or lues, or diabetic retinitis.

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To minimize the possibilities of error, a standard technique for eliciting and reading the conjunctival reactions was carefully employed. Reactions were read in fifteen to twenty minutes and were recorded as +, ++, +++, ++++. Reactions were graded primarily on the degree of injection of the ocular and palpebral conjunctivae and carnucle, and on the degree of vascular dilatation of the vessels of the limbus and conjunctiva. Subjective symptoms received little consideration in the grading of reactions.

Our aim, with the initial instillation, was to induce a moderate to marked (+++ to ++++) reaction. This reaction subsided in a few hours, and usually had disappeared by the following morning. Subsequent re-excitation or retests were performed three to seven days later. In some cases, two to six weeks elapsed between tests. Only one eye was used for the initial reaction, the other serving as control at the time of retesting. Both eyes were examined immediately prior to retesting, and the findings were recorded. A 1:10, or weaker dilution of the original strength was employed for restimulation, as quantitative differences in ophthalmic reactions were detected more easily in reactions of a slight or moderate degree. The fact that it is not unusual to obtain a "shade" of difference in the reactivity of the two eyes to the same stimulus under ordinary circumstances was taken into consideration in the interpretation of the reactions. Unless the difference between the test and control reactions was definite, the result was recorded as "no change in reactivity."

After sufficient experience, it became possible to make intermediate readings such as + ± or + + ±. Both observers read and interpreted all reactions. Observations of the reactions were made for a period of at least one hour.

By preliminary studies, it was determined that the order in which the eyes were tested was of no importance as far as the final reactions were concerned. It was also found that although some of the testing material was squeezed out of the eyes, as a result of blinking, this was not a significant factor in the final results obtained.

Where the retest reaction was stronger than the control by ± or more, a state of increased reactivity was considered to exist. When the reverse was found, i.e., the retest reaction was smaller than the control, a state of diminished reactivity or partial refractoriness was said to be present.

ANALYSIS OF CASES STUDIED

In all, one hundred and fifteen subjects were studied. The subjects were divided into four groups of cases (see Table I) as follows:

1. A group of twenty-four allergic and twenty-four nonallergic subjects, in whom the initial tests were performed with histamine and the retests with histamine.

2. A group of twenty-one pollen-sensitive cases who were tested with histamine and retested with pollen.

3. A group of twenty-three pollen-sensitive subjects who were tested and retested with pollen.

4. A group of twenty-three pollen-sensitive subjects who were tested with pollen and retested with histamine.

RESULTS

The forty-eight subjects in Group 1 were initially tested with histamine and at a later date retested with histamine. Of the 24 nonallergic subjects in this group (Table II), twelve subjects (50 per cent) showed a diminished reactivity in the eye which had been previously tested. Nine subjects (37.5 per cent) showed an increased reactivity of the ophthalmic mucous membrane in the retested eye, and three cases (12.5 per cent) revealed no change in reactivity. Of the twenty-four allergic subjects in this group, nine (37.5 per cent) showed a diminished reactivity on retest, eleven cases (45.8 per cent) revealed an increased reactivity, while four subjects (17 per cent) showed no change.

TABLE I

ANALYSIS OF CASES STUDIED

GROUP	NO. OF CASES	ALLERGIC SUBJECTS	NON ALLERGIC SUBJECTS	INITIAL EXCITATION	RE-EXCITATION AFTER 3 TO 7 DAYS
1	48	24	24	Histamine	Histamine
2	21	21	--	Histamine	Pollen
3	23	23	--	Pollen	Pollen
4	23	23	--	Pollen	Histamine
Totals	115	91	24		

TABLE II

REACTION OF OPHTHALMIC MUCOUS MEMBRANE TO RE-EXCITATION WITH NONSPECIFIC EXCITANT, HISTAMINE, AFTER PREVIOUS EXCITATION WITH HISTAMINE

RESULT	GROUP 1					
	NONALLERGIC SUBJECTS		ALLERGIC SUBJECTS		TOTALS	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
Diminished reactivity	12	50	9	37.5	21	43.75
Increased reactivity	9	37.5	11	45.8	20	41.65
No change in reactivity	3	12.5	4	16.7	7	14.6
Totals	24	100.	24	100.	48	100.

Group 2 (Table III) consisted of twenty-one allergic subjects, who were originally tested with histamine and later retested with a pollen extract. Of this group, only three cases (14 per cent) showed a diminished reactivity, whereas fourteen subjects (66.7 per cent) demonstrated an increased reactivity of the conjunctiva, while four cases (19 per cent) revealed no change in reactivity.

Groups 3 and 4 (Tables IV and V) each consisted of twenty-three allergic subjects in whom the original excitation was elicited with ragweed pollen. In Group 3, retests were made with the original excitant, whereas in Group 4, they were made with histamine. In the former group, ten subjects (43.5 per cent) revealed a diminished reactivity, 10 subjects (43.5 per cent) revealed an increased reactivity, and three subjects (13 per cent) showed no change in reactivity. In Group 4, ten of the twenty-three subjects studied (43.5 per cent) demonstrated a diminished reactivity; eleven subjects (48 per cent) revealed an increased reactivity; whereas two subjects (8.5 per cent) showed no change in reactivity. The results of all the studies are summarized in Table VI.

TABLE III

REACTION OF OPHTHALMIC MUCOUS MEMBRANE TO RE-EXCITATION WITH SPECIFIC EXCITANT, RAGWEED, AFTER PREVIOUS EXCITATION WITH NONSPECIFIC EXCITANT, HISTAMINE

RESULTS	GROUP 2	
	NO. OF CASES	PER CENT
Diminished reactivity	3	14.3
Increased reactivity	14	66.7
No change in reactivity	4	19.
Totals	21	100.

TABLE IV

REACTION OF OPHTHALMIC MUCOUS MEMBRANE TO RE-EXCITATION WITH SPECIFIC EXCITANT, RAGWEED, AFTER PREVIOUS EXCITATION WITH SPECIFIC EXCITANT, RAGWEED

RESULT	GROUP 3	
	NO. OF CASES	PER CENT
Diminished reactivity	10	43.5
Increased reactivity	10	43.5
No change in reactivity	3	13.
Totals	23	100.

TABLE V

REACTION OF OPHTHALMIC MUCOUS MEMBRANE TO RE-EXCITATION WITH NONSPECIFIC EXCITANT, HISTAMINE, AFTER PREVIOUS EXCITATION WITH SPECIFIC EXCITANT, RAGWEED

RESULTS	GROUP 4	
	NO. OF CASES	PER CENT
Diminished reactivity	10	43.5
Increased reactivity	11	47.8
No change in reactivity	2	8.7
Totals	23	100.

DISCUSSION

The time interval between test and retest was usually three to seven days. However, it appeared that slight variation in the time interval had little direct bearing on the end result. This was illustrated in the case of one nonallergic subject in whom the histamine test was repeated after an interval of forty-three days, and a state of diminished reac-

tivity was still present. In another instance, where ragweed was the initial test, a retest with histamine in twenty-four days showed a state of increased reactivity. In two cases there was a time interval of only one day. In one of these subjects in whom histamine was used for primary and secondary testing, the reaction after retest was equal to the control. In the other subject, similarly tested, a state of increased reactivity was found to exist.

No reliable information could be derived from a comparison of the retest reactions with the original reactions because of the differences in testing conditions which involved variations in excitants, materials, time, and in the quantities used.

TABLE VI

SUMMARY

	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Initial excitation	Histamine	Histamine	Pollen	Pollen
Re-excitation	Histamine	Pollen	Pollen	Histamine
No. of cases (allergic)	48	21	23	23
Per cent diminished reactivity	44	14	43.5	43
Per cent increased reactivity	42	67	43.5	48
Per cent no change in reactivity	14	19	13	9

The results obtained in these studies differ in certain respects from those of Bowman and Walzer.[1] In their studies on the response of cutaneous sites to restimulation, they studied wheal formation, particularly the amount of edema involved in the reaction. In the present study of ophthalmic reactions, we were primarily measuring the degree of vascular dilatation. It is extremely difficult to estimate degrees of edema or capillary permeability in ophthalmic reactions unless the reactions are quite marked. The vascular dilatation of the conjunctival reaction may, to some extent, be the counterpart of the erythematous response in the cutaneous reaction. In this connection, it is interesting to note, that in Bowman and Walzer's cases, the surrounding areola or erythema was diminished in all reactions resulting from re-excitations of tested sites. This decrease was least pronounced when histamine wheal sites were retested with the specific excitant, ragweed. In our own studies, histamine stimulation followed by ragweed reexcitation was also the sequence in which diminished reactivity occurred least frequently.

To draw any conclusions as to the clinical significance of our findings in these studies would be premature at this time, in view of the limited amount of information available. Further study of the problems involved is now in progress.

SUMMARY

When the ophthalmic mucous membrane is stimulated with a nonspecific excitant, histamine, and restimulated after three to seven days

with a specific substance, ragweed, there is an increased vascular response in the form of vascular dilatation in 67 per cent of cases. Under similar testing conditions, restimulation of a histamine site with histamine produces no consistent change in reactivity, nor does any change in vascular response result when the initial excitation is specific.

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DISCUSSION

DR. MATTHEW WALZER.—In discussions of constitutional reactions occurring in hay fever patients receiving conservative dosage, there is a tendency to focus attention upon antibodies of one kind or another as the responsible factor. A high reagin concentration, the presence of heterophile antibody, and absence of the thermostabile antibody represent some of the explanations which have been offered for these reactions. Although some of these factors undoubtedly are involved, too little attention has been given to the shock tissue factor in such phenomena. By showing that the ophthalmic mucous membranes in patients with repeated constitutional reactions tend to manifest a degree of reactivity which is abnormally high when compared to cutaneous sensitivity in the same patients, Sherman and Baron again stress the importance of the role of the shock tissue in allergic phenomena.

The authors have devised a crude technique for comparative titrations of the ophthalmic and cutaneous sensitivities in the same patient, but they are not prepared to offer this as a practical procedure for ophthalmic titration and for the prevention of constitutional reactions. Ophthalmic titrations are subject to many more technical limitations than are cutaneous titrations. One great handicap is that only two conjunctivae are available in each patient for titration, and good technique does not permit retests of these surfaces at frequent intervals. Sherman and Feldman have shown that conjunctival responses may be altered for variable periods of time following ophthalmic reactions caused by allergic excitants (pollens, danders, etc.) or by nonspecific (histamine, dionin, etc.) substances. Under the circumstances, a quantitative technique which is based upon repeated testing of the ophthalmic or other mucous membranes, at short intervals, is subject to considerable error. This situation is not unlike that which obtains in the skin when retests of the same cutaneous site are made at frequent intervals.

A QUANTITATIVE METHOD FOR MEASUREMENT OF PRECIPITIN REACTIONS

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IN 1943, Hampton et al.[1] described a precipitin method for detecting "thermostable" antibody in the sera of patients treated with ragweed pollen extract. The values of the end points of their experiments were in terms of arbitrary interpretations of the usual flocculation technique (i.e., +, ++, +++, ++++). These were realized to be far from accurate. It became desirable to detect slight changes, if possible, in the amount of free antigen reacting with antiragweed rabbit serum. An investigation was therefore undertaken to find a quantitative precipitin method. Various similar attempts had been undertaken.

In 1904, Nuttall[2] devised a method for measuring the sedimentation of precipitate after several days' standing in capillary tubes. Schur[3] modified Nuttall's technique by centrifugation in closed capillaries after incubation. Hamburger[4] made additional modification by using very carefully graduated capillary tubes. Since these procedures were too time consuming when a large number of readings were to be made and presented the very obvious difficulty in cleaning the closed capillaries, Boyden and Baier[5] and Baier[6] used Van Allen thrombocytocrits for the quantitative determination of precipitate. These investigators studied variations in amount of antigen per given concentration of serum and variations in temperature, length of incubation, and rate of centrifugation. The use of Van Allen tubes requires special clips and centrifuge accessories; these are moderately expensive, especially when large numbers are needed. Jones and Little[7] by using capillary centrifuge tubes, studied the volume of precipitate with respect to zone of maximum precipitation with optimum ratios of antigen and immune serum.

An inquiry concerning the adaptability of other available sedimentation tubes was made (i.e., Goetz, Bauer-Schenck, Hopkins), but none was satisfactory. The desired essential characteristics of a tube for our purposes were (1) that the mixture of antigen and antibody, precipitin reaction, and centrifugation be carried out in the same tube, thus avoiding transference of material; (2) that the bore of the capillaries be small enough to make the available precipitate reliably measurable; (3) that the capillaries be easily cleaned; and (4) that the tubes be of simple construction and therefore relatively inexpensive and available in large numbers.

Meloche and Yen[8] designed a microcentrifuge tube* for the quantitative measurement of small amounts of precipitate in the determination

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*Corning Pyrex No. 8065.

of phosphorus in iron and other inorganic precipitates. This tube fulfilled all the requirements listed above.

The original method of sealing the capillaries of these tubes involved the use of a globule of mercury in order to balance the volume of fluid within the tube. The mercury was placed in the bottom of an outer 15 c.c. centrifuge tube. After centrifugation, the Meloche tube was very carefully removed from the outer tube and the precipitate was measured.

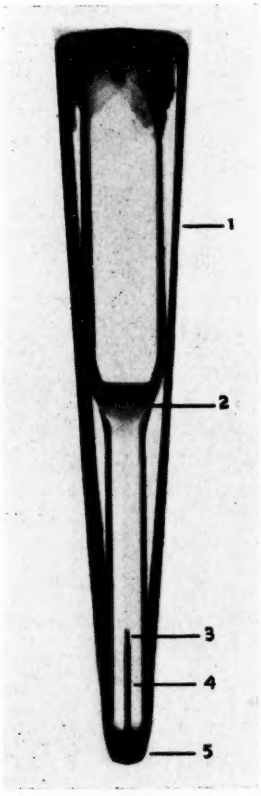

Fig. 1.—*1*, Rubber band; *2*, supernatant; *3*, precipitate; *4*, mercury; *5*, paraffin coating.

Since the procedures of our experiments involve very vigorous handling after sealing, the original method was unsatisfactory. A modification was made, as follows:

METHOD

Mercury is drawn into the capillary from the tip by means of mild suction to a height of 15 to 20 mm., and the tip is sealed with paraffin.

The antiserum and antigen are added in the desired quantities (in our experiments 0.25 c.c. each) to the upper cupped portion of the

tube. A wide rubber band (1 cm.) is placed lengthwise around the tube. This tightly seals the capillary tip. Rubber bands are necessary as paraffin alone is insufficient to prevent the mercury and fluid from escaping from the capillaries during centrifugation. The tubes are placed in a test tube rack, put in an automatic shaker for two minutes, incubated at 37° C. for one hour, and allowed to stand in a refrigerator overnight.

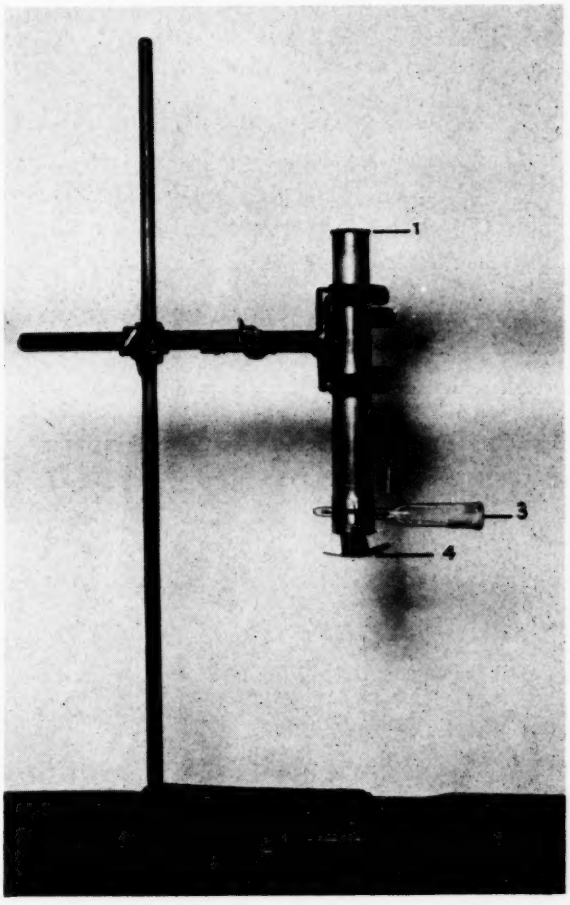

Fig. 2.—*1*, Eyepiece containing micrometer scale; *2*, lens; *3*, Meloche tube; *4*, shield.

The tubes are then placed in ordinary metal centrifuge cups (for 15 c.c. tubes) with cotton packed at the bottom to prevent undue movement during centrifugation. The cups are fitted into a regular centrifuge head in which the tubes swing horizontally. Centrifugation at 2,500 revolutions per minute is carried out for fifteen minutes. The centrifuge is then stopped and each tube turned 180° and recentrifuged at 2,500 revolutions per minute for fifteen minutes. The tubes are thus rotated to reduce the slant of the precipitate while packing. This particular speed and time of centrifugation and interval of rotation

were finally selected, since they were found to produce the optimum packing of the precipitates regardless of quantity of flocculation.

After centrifugation, the bands are removed and the capillary portion of the tubes is inserted in a simple optical apparatus.

The apparatus consists of a metal cylinder having a lens system (with a magnification of 22) at one end and two holes at the point of focus for insertion of the stem of the Meloche tube at the other end. There is a micrometer scale in the upper eyepiece. A black round disk (slightly larger in diameter than the cylinder) is attached by stems from the open end of the cylinder at a distance of about 2 cm. The screen is needed to prevent light from passing directly through (at right angles) the tube and precipitate. The light thus enters from the sides so that the precipitate, which should be approximately in the center of the cylinder, reflects the light into the scale and appears like a heavy white mass on a dark background with the scale distinctly illuminated and easy to read.

TABLE I

CALIBRATIONS OF STANDARD TUBES

TUBE NO.	DIAMETER	FACTOR πr^2	TUBE NO.	DIAMETER	FACTOR πr^2
1	0.65	3.31	25	0.65	3.31
2	0.66	3.42	26	0.66	3.42
3	0.67	3.52	27	0.65	3.31
4	0.655	3.36	28	0.66	3.42
5	0.67	3.52	29	0.65	3.31
6	0.66	3.42	30	0.65	3.31
7	0.66	3.42	31	0.65	3.31
8	0.69	3.735	32	0.68	3.63
9	0.62	3.015	33	0.66	3.42
10	0.65	3.31	34	0.67	3.52
11	0.65	3.31	35	0.615	2.955
12	0.66	3.42	36	0.66	3.42
13	0.63	3.11	37	0.67	3.52
14	0.65	3.31	38	0.65	3.31
15	0.69	3.735	39	0.69	3.735
16	0.71	3.96	40	0.69	3.735
17	0.68	3.63	41	0.62	3.015
18	0.66	3.42	42	0.655	3.36
19	0.645	3.26	43	0.61	2.95
20	0.64	3.20	44	0.69	3.735
21	0.62	3.015			
22	0.66	3.42			
23	0.67	3.52			
24	0.615	2.955			

Meloche tubes lot No. 1.

Each tube is calibrated with mercury to determine the bore of the capillary. The average diameter of the capillary of the tubes in the lot available to the laboratory was 0.65 mm.

The length of the precipitate is computed from the reading obtained on the micrometer scale by dividing by the magnification of the ocular system. Then the volume of the precipitate is calculated by multiplying the length of the precipitate by πR^2. For example:

Calibrated diameter of tube in use = 0.65 mm.
Magnification of optical system = 22
Length of precipitate as read = 35 micrometer units
Actual length of precipitate $= \frac{35}{22} = 1.59$ mm.
$R^2 = (\frac{1}{2} \times 0.65)^2 = 1.055$
Volume of precipitate in c.mm. $= 1.59 \times 3.1416 \times 1.055 = 5.26$ (π)

TABLE II

COMPARISON OF READINGS OF PRECIPITIN REACTIONS BY CONVENTIONAL AND QUANTITATIVE TECHNIQUES

STRENGTH OF ANTIGEN* (PROTEIN NITROGEN UNITS)	ESTIMATED FLOCCULATION		VOLUME OF PRECIPITATE (CUBIC MILLIMETERS)
Control	0		0
50	±		0
100	+		0.80†
			0.78
150	+		1.86
			1.69
200	++		1.93
250	++		2.25
			2.33
300	+ ++		2.56
			2.72
400	++++		3.59
			3.74
500	++++		4.04
			4.12
600	++++		4.35
			4.87
700	++++		5.06
			5.13
800	++++		4.80
			5.36
1000	++++		5.27
1500	++++	Progressively heavier precipitate	8.12
			8.25
2000	++++		9.75
			9.75
2500	++++		10.20
			10.60

*Ragweed added to antiragweed rabbit serum.
†Tests done in duplicate.

DISCUSSION

Measurement by this method must be considered as the apparent volume of the precipitate rather than the absolute volume. If all conditions of the reactions and centrifugation are uniform in successive experiments, good checks and comparative values can be obtained.

Table II shows comparative values of precipitates formed by mixtures of antiragweed rabbit serum and low ragweed antigen dilutions, evaluated by the flocculation technique and by measurement in the Meloche tube. This table clearly illustrates how the quantitative measurement

can detect changes in the amount of precipitate which would not be observed by the flocculation method. Should these changes not be noted, significantly varying amounts of precipitate might all be classified in the same category.

It was also noted that reliable values could be obtained with slightly opalescent or turbid sera (which would not clear after high centrifugation) unless contamination by bacteria was present. Precipitins in such opalescent sera could not be evaluated by the flocculation method.

SUMMARY

1. A technique is described wherein the Meloche microcentrifuge tube is used for the quantitative measurement of precipitate formed by the precipitin reaction.

2. The method is reliable and relatively simple and has possibilities of being applicable to the measurement of precipitates in other immunologic reactions.

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BLOOD STUDIES IN ALLERGY

I. The Direct Counting Chamber Determination of Eosinophils by Propylene Glycol Aqueous Stains

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THE present method of determining the number of eosinophils in the blood requires both a differential white blood count and a total leucocyte count. The percentage of eosinophils obtained from the differential is applied to the total number of leucocytes to determine the number of eosinophils per cubic centimeter of blood. This method is not only time consuming but inaccurate, as it totals the errors inherent in the two procedures.

The errors of greatest magnitude appear to be found in the technique of the differential count. These may be classified according to Barnett[1] as the mechanical error which includes all variations in taking the blood sample, irregularities in the distribution of cells resulting from the method of preparing the film, and the areas over which the count is made; and, secondly, the accidental or sampling error.

The distribution of white cells varies in different parts of the film, with a higher incidence of polymorphonuclear cells and monocytes at the edges and tail of the preparation.[2-5] As differences in cell size appear to be the fundamental cause for this irregular distribution,[2, 6, 7] one would also expect an increase of eosinophils at the margins of the film. MacGregor, Richards, and Loh,[5] using the slide technique, found certain differences in the number of eosinophils between areas of the film, but the nature of this variation was not clear and it did not occur as regularly as with polymorphonuclear cells and lymphocytes. Sturgis and Bethell[8] are of the opinion that the distribution of white cells is more nearly uniform in cover slip than in slide preparations. They conclude, however, in their most recent review of the subject, that no agreement has been reached regarding the preferred method of differential counting or the degree to which the distribution of cells approaches the wholly accidental on either slide or cover slip films.

It, nevertheless, remains a common experience to find significant variations in the percentage of eosinophils from repeated counts of the same cover slip preparation. Whether this variation is due in part to the selective distribution of eosinophils or due entirely to their chance distribution is undetermined. Because of the small number of eosinophils ordinarily counted, the chance of accidental error persists as a

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major factor in the accuracy of eosinophil counts as determined from either the slide or cover slip preparation.

The fragility of the eosinophil makes it peculiarly susceptible to variations in trauma or pressure in preparing the film. With a normal number of eosinophils, the presence of an occasional disrupted cell does not interfere with the accuracy of the count. In cases of eosinophilia, this factor assumes greater importance.

The errors pertaining to the total white counts have been recently reviewed.[8-11] It appears to be the consensus of opinion that when the conditions of leucocyte enumeration are adequately controlled, the accidental distribution of cells in the counting chamber remains the only important variable.[11]

From this appraisal of errors inherent in the procedure, it is apparent that the present indirect method of counting eosinophils is potentially inaccurate. The absence of a reliable direct method of enumerating these cells may be in part responsible for the paucity of knowledge regarding the function of eosinophils.

Dunger[12] in 1910 attempted the direct enumeration of eosinophils by the use of a diluting fluid of:

1 per cent Aqueous eosin solution	10 c.c.
Acetone	10 c.c.
Aqua destillata ad	100 c.c.

In this medium the eosinophilic granules stained bright yellow to ruby red. The diluent was not satisfactory for determining the total leucocytes, as these cells rapidly faded and became "shadows." This diluent was used by von Domarus,[13] who emphasized the value of determining the absolute eosinophil count. He also advised against attempts to count the leucocytes in the same chamber.

Camara and Alvarez[14] used a modification of this diluent in the direct enumeration of eosinophils:

1 per cent Aqueous eosin	5 c.c.
Acetone	5 c.c.
Aqua destillata	100 c.c.

This diluent has also been used by Squier and Madison[15] to count eosinophils in their modification of the leucopenic index originally decribed by Vaughan.[16]

In a further study of this method we have found that it is not well adapted for counting of eosinophils or for use in determining the total leucocyte count. When used as a white blood cell diluting fluid, as described by Squier and Madison,[15] the eosinophils invariably rupture, leaving a "ghost" form containing the stained eosinophilic granules.

When studied in the counting chamber under oil immersion (using a thin cover slip instead of the standard counting chamber cover), the

following changes may be observed within a period of three minutes: There is an initial swelling of the cell followed by disruption of the limiting membrane, leaving a crescent-shaped mass of clumped granules. The eosinophilic granules stain bright red, serving to identify the cell.

The total leucocyte count as determined by the eosin-acetone-aqueous diluting fluid is usually lower than a parallel count using the standard acetic acid diluent. Repeated determinations from the same counting chamber field are apt to result in a further diminution of the total count. The leucocytes remain refractile and clearly visible for approximately two minutes, after which time they suddenly fade. When observed under oil immersion, as described above, a progressive enlargement of the leucocyte occurs during the first two minutes of contact with this diluent; occasionally a bud may develop on the periphery of the cell. Rupture of the limiting membrane with a discharge of cytoplasmic granules occurs in the majority of instances within a period of two to three minutes. This change in the structure of the leucocyte is associated with the loss of the cell's ability to refract light in the microscopic field and accounts for its rapidly diminishing visibilty.

If the eosin in this diluent is replaced by a smaller amount of a basic stain such as methylene blue, one may observe the movement of nuclei as the polymorphonuclear or mononuclear cell ruptures. As a rule, the nucleus is pushed to the opening in the cell membrane and occasionally it may be extruded.

Because of these variations in the total leucocyte count occurring with time, it is necessary to make the determination immediately after mixing the blood with the diluent. Even so, rupture and fading of the leucocytes are apt to take place before the cells in the four squares of the counting chamber can be enumerated.

The disruption of eosinophils and other leucocytes in this diluent appears to be the direct result of its hypotonicity. Attempts were made to secure a solution more nearly isotonic by the addition of electrolytes. This, however, was not feasible, as the addition of sodium chloride or other ions either interfered with the staining of eosinophils or did not permit hemolysis. Altering the content of acetone was ineffective. In fact, acetone might be omitted without a definite change in the behavior of the cells.

A search was made for some nonionizable substance miscible with water and possessing the ability to hemolyze red cells and acting as a base for stains. The following organic solvents were tried:

Ethylene glycol	Methyl alcohol
Ethylene glycol monomethyl ether	Ethyl alcohol
Ethylene glycol monoethyl ether	Amyl alcohol
Ethylene glycol monobutyl ether	Capryl alcohol
Diethylene glycol	Glycerol
Diethylene glycol monomethyl ether	Dextrose
Diethylene glycol monoethyl ether	Sorbitol

Diethylene glycol monobutyl ether	Isopropyl alcohol
Triethylene glycol	Acetic acid
Tetraethylene glycol	Acetone
Propylene glycol	Methyl acetate
Dipropylene glycol	Formic acid
Trimethylene glycol	Formamide
	Lactic acid
	Ethyl lactate
	Ethylene diamine
	Triethanolamine
	Urea
	Dioxane

Propylene glycol was found to be most advantageous. The use of equal parts of propylene glycol and distilled water as a white blood cell diluting fluid has been described in an earlier report.[17]

A propylene glycol-aqueous diluting fluid possessed many technical advantages in comparison with the standard acetic acid diluent, because of its greater viscosity, its slower rate of evaporation, and its ability to act as a solvent for both acid and basic dyes. Its use permitted the differential staining of eosinophils, polymorphonuclear and mononuclear cells in the counting chamber, affording a direct method of enumerating eosinophils in the same sample of blood used in determining the total leucocyte count.

Propylene glycol in a 50 per cent aqueous solution at room temperature has the ability to cause the red blood cells to fade or to become relatively nonrefractile within a period of five minutes. Although a true hemolysis does not occur, the ghost forms of the erythrocytes do not interfere with the staining or enumeration of leucocytes. A study of the peculiar effect of propylene glycol on erythrocytes will be reported elsewhere.[18]

Propylene glycol proved superior to other solvents with the possible exception of a 35 per cent solution of dipropylene glycol in water, which had approximately the same properties as 50 per cent propylene glycol. Ethylene and triethylene glycol served as adequate solvents for stains, but when used in various concentrations did not permit as rapid or as complete fading of erythrocytes or did not allow as clear staining detail as a 50 per cent solution of propylene glycol.

As originally reported, the stain consisted of two solutions which were mixed in equal parts immediately prior to use. Solution 1 consisted of 0.1 Gm. methylene blue in 100 c.c. propylene glycol; solution 2 contained 0.1 Gm. eosin B dissolved in 100 c.c. distilled water.

Other xanthine dyes (eosin Y, ethyl eosin, erythrosin B, phloxine, and rose bengal) were substituted for eosin B. Phloxine was found to be the most effective of the group. Equally good, if not superior, staining qualities of eosinophils were obtained with one-half the content of phloxine as required for eosin B. Furthermore, in the presence of

phoxine, one-half the amount of methylene blue was required to give approximately the same degree of basic staining. The revised stain is prepared as follows:

Given amounts of stock solutions containing 0.1 per cent methylene blue in propylene glycol and 0.1 per cent phloxine in propylene glycol are each diluted with an equal volume of distilled water and placed in dropper bottles. For example:

Solution 1		Solution 2	
0.1 per cent methylene blue in propylene glycol	50 c.c.	0.1 per cent phloxine in propylene glycol	50 c.c.
Distilled water	50 c.c.	Distilled water	50 c.c.

The final white blood cell diluting fluid is made by mixing an equal number of drops of Solution 1 and Solution 2* in a test tube. This remains usable for approximately four hours; after standing for longer periods, differential staining detail may be impaired and precipitation of dyes may occur. Counts are made in the standard counting chamber. If the chamber is filled immediately after diluting and mixing, a period of five minutes is recommended for fading of the red cells and settling of the leucocytes. A total period of ten to fifteen minutes is required for maximum staining of cells. Mixed blood may be left in the pipette overnight and counted the next day without deterioration in the staining qualities of the cells or a significant variation in the total count. With this preparation, the granules of the eosinophil stain brilliant red but allow the green-staining nuclei of the cell to be seen. The nuclear elements of all white cells take an emerald green stain and are sharply differentiated from the clear cytoplasm of the cells. The limiting cell membranes are clearly visible.

Other fluoran derivatives of the xanthine dyes may be used. Rose bengal in the same concentration as phloxine stains the eosinophils slightly darker but does not permit as sharp a differentiation between the nucleus and cytoplasm of the polymorphonuclear cells. Eosin Y may be used in higher concentration but because of its yellow color it is not recommended. Ethyl eosin and erythrosin B are not satisfactory.

A search for basic dyes other than methylene blue was also made. Two or three representative members of each chemical group were studied. The majority was soluble in the glycols, but methylene blue was judged to be the most effective when used in combination with members of the eosin series for counting chamber differentiation of cells.

The Romanowsky stains (Wright's, Giemsa) which utilize a chemical combination of methylene blue and eosin (methylene blue eosinate) were

*After the diluted phloxine in glycol stands in a dropper bottle six to eight weeks it becomes slightly less effective as an eosinophil stain. This may be remedied by preparing Solution 2 from the stock at monthly intervals or by using a larger amount of Solution 2 in the final mixture, in case the eosinophils do not stain sharply.

Because of the variation in staining ability between lots of dyes, optimum acid and basic staining may possibly be obtained by making a change in the proportion of Solutions 1 and 2 in the final diluent. For example, four parts of Solution 1 and six parts of Solution 2 might result in a better stain than if equal parts of the two were mixed.

not readily soluble in 50 per cent propylene glycol and did not produce adequate staining of cells.

In the presence of 50 per cent propylene glycol in water, the eosinophil undergoes a peculiar change. The capsule of the cell gradually swells until a capsular tumor approximately the size of the original eosinophil may be present to one side of the cell. This capsular enlargement does not distort the body of the eosinophil and in no way interferes with the identification of the cell. A similar, although less marked, change occurs with other members of the leucocyte series. A detailed study of these morphologic changes will be reported.[19]

A comparison of the counting chamber differential count and the differential count from the Wright-stained film on a series of twenty normals has been published.[17] On a given blood there might be considerable variation in the number of eosinophils as determined by the two methods, but the variation was not in a constant direction and the sums of the eosinophils enumerated by the two methods were approximately the same.

TABLE I

CASE	P. G. STAIN PER CENT	FILM DIFF. PER CENT	CASE	P. G. STAIN PER CENT	FILM DIFF. PER CENT	CASE	P. G. STAIN PER CENT	FILM DIFF. PER CENT
W. G.	9	13	F. M.	20	20	H. B.	8	5
H. F.	17	17		13	15		9	2
V. B.	1	3		20	15		5	6
I. K.	1	2		17	16		5	8
M. L.	17	21		14	11		6	6
J. D.	0	0		11	11		2	5
S. L.	11	9	E. R.	7	1		6	3
J. S.	4	4		5	6		4	5
W. Y.	0	0		6	3		11	4
F. W.	7	8		2	4		4	8
J. E.	1	0	L. M.	12	16		10	2
I. G.	2	1		13	11		1	2
W. H.	5	5		7	7		8	8
D. H.	11	7		14	14	B. D.	11	17
D. N.	5	4	M. S.	10	9		12	15
H. K.	6	3		6	1		7	12

Similar findings were observed in performing eosinophil counts in a series of allergy patients (Table I)). In this series 100 leucocytes were counted by each of the two methods. A standard technique of preparing the film was selected, and the count was started at the mid-point of the tail of the film, the field was then moved to the periphery, carried along the edge for a short distance, then continued in a zigzag fashion over the selected half of the preparation, approaching the head of the film with each cross movement.

It is quite possible that more than one hundred white cells should be counted in the counting chamber enumeration of eosinophils. This point remains to be determined. Because of the small number of eosinophils present in normal blood, it is obvious that merely the enumeration of the eosin-staining cells in the four corners of the standard counting

chamber would not be an accurate procedure. An alternative, should one not be interested in the relative numbers of other cells, would consist of counting all the eosinophils enclosed within the ruled portion of the counting field and multiplying the number obtained by 22.2 to secure the number of eosinophils per c.c. of blood. If blood is drawn to the 1 mm. mark of a while cell pipette prior to the addition of diluent, double the number of eosinophils may be observed. In this case, the number of eosinophils per nine squares multiplied by 11.1 will give the total number of cells per c.c. of blood.

DISCUSSION

The differential staining of eosinophils in the counting chamber permits an eosinophil count on the same specimen of blood used in determining the total number of leucocytes. This results in a minimum possible error in comparison with the alternative procedure of determining the percentage of eosinophils from a differential white count and applying this value to the total white cell count to determine the number of eosinophils per c.c. of blood. The direct method of counting eosinophils retains the chance error, but this is unavoidable with any technique dependent upon sampling. It avoids the additional mechanical and distributional errors inherent in preparing and estimating the differential count by using the stained film preparation.

The diluting fluid of phloxine and methylene blue in equal parts of propylene glycol and water is distinctly superior to the acetone-eosin-water mixtures used by earlier investigators. The eosinophils are more clearly observed, and other leucocytes remain stable and clearly visible for long periods of time in the former in contrast to the rapid changes occurring in the structure and visibility of white cells in the latter diluent.

The use of phloxine appears to be an improvement over the previously described eosin B, in that one-half the amount of dye gives equally good staining of eosinophils. Furthermore, in the presence of phloxine, the content of methylene blue may be reduced 50 per cent without impairment of basic staining.

SUMMARY

A white cell diluent of phloxine and methylene blue dissolved in equal parts of propylene glycol and water permits the counting chamber differentiation of eosinophils on the same specimen used in determining the total leucocyte count.

This technique has numerous advantages in comparison with previously described direct methods of enumerating eosinophils and would appear to be more accurate than the indirect method now in general use.

I wish to acknowledge the technical assistance of Elizabeth Barber Gibson and the helpful suggestions of Dr. Robert Parsons.

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WEATHER AND DEATH IN ASTHMA

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WHILE we may accept the important role of specific sensitization in asthma, it is obvious to every clinical observer that other environmental factors, effective in altering the organic state of the patient, must be considered in the constellation of events that initiate the attack or alter its course, either favorably or unfavorably. The very fact that under normal conditions the attack is self-limited supports the view that changes in the organic state (endocrine, chemical, or nervous) must be responsible. We may accept, too, the particular significance of smooth muscle tone in the underlying mechanism of both asthma and the closely related dysfunction, mucous colitis.

In both instances smooth muscle spasm in the wall of the bronchus or the wall of the colon results in anoxia. This anoxia is first followed by undue stimulation of the local glands (with consequent secretion of the characteristically thick, glairy mucus); later by local necrosis. In the bronchus this situation is obviously of critical importance, in the colon of much less significance. Relief from this situation probably occurs when the local anoxia reaches a point where the tissues become relatively acid. The smooth muscle then relaxes its tone (i.e., it is actively stimulated); this may proceed to fatigue, with undue dilatation.

Quite apart from superimposed specific autonomic nerve control of such smooth muscle, the biochemical change in the local tissue status (involving local ganglia, smooth muscle, epithelium, connective tissue, and vessels) is associated with and follows change in the local oxygen supply.

The general organic status is conditioned by many factors: age, activity, diet, the genotype, and, as becomes very evident in the allergic state, by season and by weather. Granting the initiation by specific factors, the progress of the attack and its final outcome will be greatly modified by these forces that govern the general organic status, and the neglect of their consideration by the physician is a serious reproach.

In a recent paper, one of us[1] published a series of case records of fatal asthmatic attacks, and, using additional records generously placed at our disposal by Hilding[2] of Minneapolis, we have examined the clinical course of these patients as related to the major changes in the meteorological environment (temperature, barometric pressure, precipitation). One of us[3] has previously pointed out the great autonomic lability of the allergic patient and the frequent association of death in asthma with passage of major polar air masses.

Hilding has studied in great detail the changes that occur in the ciliated epithelium of the bronchi and has illustrated the changes in a series of fatal cases recently published. His study is of particular significance in making evident the complexity of the problem that is presented when we seek to unravel the components, constitutional, allergic, environmental, infectious; the hypertrophy and atrophy and metamorphosis of local tissues, and all this on the background of autonomic dysfunction, with its interrelation of psychic, endocrine, biochemical, and neuromuscular factors.

As a result of the local changes that occur with metamorphosis in the smaller bronchi, the ciliary mechanism is lost; the difficulty of removal of the secretion is aggravated because the mucus remains attached over large areas to the cells that produce it, thus anchoring the mass to the wall. When the air passages have become sufficiently filled, the patient dies of asphyxia.

In Hilding's opinion, and the opinion is based on very sound histopathologic evidence, this metamorphosis is the chief pathologic change, and death may be attributed to the loss of ciliary function.

VAUGHAN CASES

We turn first to the case record of V. F., a girl described in detail in the preceding paper[1] and who had attacks as follows:

1. The night of October 8, 1940.
2. During the week ending November 9, 1940 (with her period).
3. February 25, 1941, following a head cold and lasting until about March 5, 1941.
4. May 11 and 12, 1941, following a "head cold."
5. August 14, 1941, after having had her hair washed and gone to an air-conditioned movie.
6. The night of October 16, 1941 (no etiologic factor such as catamenia, head colds, etc.).
7. November 22, 1941 (this attack commenced about November 18, at least no earlier than the eighteenth, and was very severe. She became adrenalin-fast but responded to aminophylline. The attack cleared up about November 28).
8. The night of February 15, 1942. This was her final attack.

She usually had some wheezing (every day), and was usually worse with the catamenia.

A meteorogram has been prepared to illustrate the environmental situation as far as temperature and barometric pressure were concerned at the time of these attacks (Fig. 1). In this meteorogram the upper curve represents the maximal and minimal daily temperature (solid field); the lower curve, the barometric pressure, in inches; and at the base line, precipitation is indicated by solid blocks. The dates of the individual episodes are indicated by circled numbers.

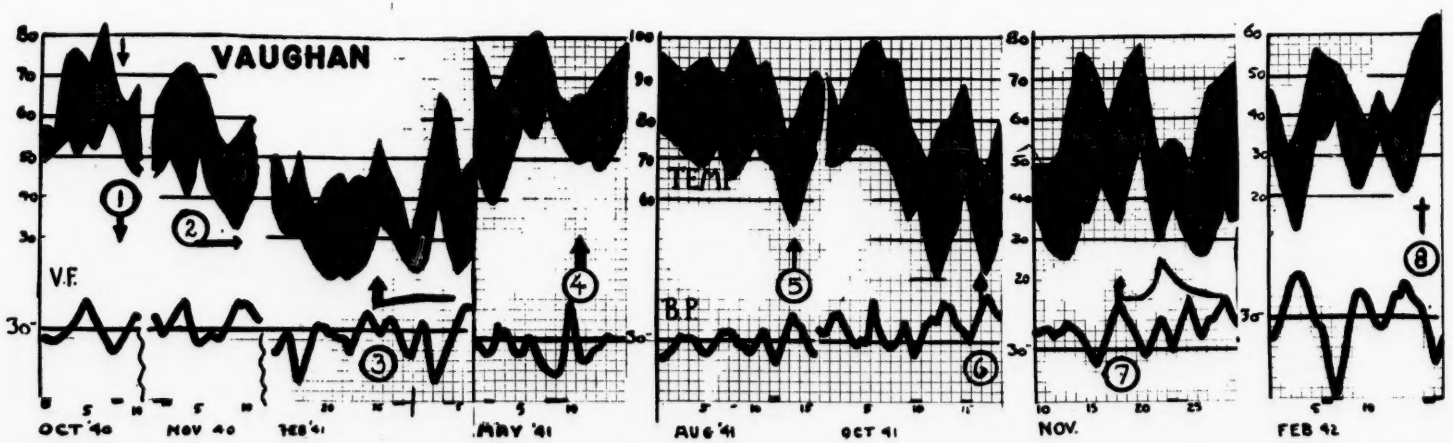

Fig. 1.—Meteorogram to illustrate asthmatic attacks and death in patient V. F. (Case 1) of Vaughan series. Environmental temperatures, maximal and minimal, are indicated in the solid black field. Barometric pressure (scale in inches) is indicated by the solid line; precipitation, by black blocks below the date line.

It will be observed that the first attack occurred with a sharp decline from high environmental temperatures. There was rain at this time, with high humidity, and a sharp decline in barometric pressure. With the menstrual period and with declining temperatures, episode 2 occurred. The third attack occurred with a head cold; this was associated with the passage of cold air masses after the barometric low of February 17. The asthmatic attack began with a temperature crest and high humidity. Episodes 4, 5, and 6 occurred with the passage of a cold air mass. Quite similar to 6 was attack 7, and it was accentuated with the passage of a succeeding barometric crest. Death occurred immediately in the wake of a secondary barometric crest after unusually low barometric pressure on February 7.

Case 2 died at 9:30 P.M., April 18, 1933. Three days before the death of the patient, a rhinologist probed the frontal sinuses and this may have caused activation, although she was up and around until the onset of the severe attack twenty-four hours prior to her death.

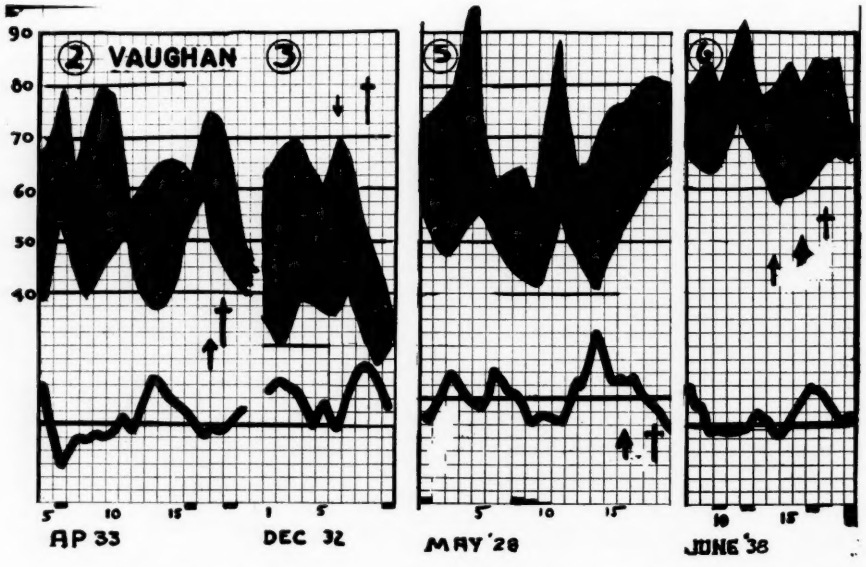

Fig. 2.—Meteorogram to illustrate asthmatic attacks and deaths in Cases 2, 3, 5, 6 of Vaughan series.

When we examine the meteorogram (Fig. 2) it will be noted that in this case the attack occurred immediately after a barometric low on April 17, at which time a temperature crest had been reached. Death occurred the following day at a cyclonic interface, with precipitation and the beginning of temperature decline.

Case 3 had constant asthma and was adrenalin-fast. In her final illness, she became much worse on December 6, 1932, and died at 11:30 A.M. on December 9. Here the picture is similar environmentally to that of Case 2. The onset of the attack occurred at a time of low barometric

pressure, and death followed with the succeeding polar episode at a time of high barometric pressure.

Case 5 had her final attack commencing on May 16, 1928, and died during the night of May 18. In this instance, examination of the meteorogram reveals a high barometric pressure crest on the fourteenth of the month. The initiation of the asthmatic attack in the wake of this, with rising temperature, and final death during the course of the passage of a cyclonic air mass should be noted.

Case 6 was progressing satisfactorily on June 10, 1938. On June 14, she was having a little more asthma. On June 16, this was severe enough to require aminophylline twice during the night; it became more severe after midnight on June 16. Her physician was called at 3 in the morning, and she died at 3:30 P.M. on June 18. Here the attack was initiated at a time when temperatures had declined very sharply from more than 90° F. The severity of the attack increased with increasing barometric pressure, and death occurred immediately in the wake of this crest.

HILDING RECORDS

Dr. Hilding has placed at our disposal the case records of the following individuals who died in acute attacks (Fig. 3):

CASE 1.—Mrs. J. S. B., 68 years of age, died on May 31, 1939, at 10:55 P.M. She commenced having asthma six years previously. She took an orange treatment under a doctor in Los Angeles, and lost weight and strength, and was also treated by a doctor in Kansas City. Asthma was more or less constant at all seasons. On the day of her death she felt that she was developing a cold, complained of weakness, and her heart rate was 120. At 6 P.M. she was cyanotic and at 9 P.M. she was unconscious. She had had a slight stroke a year before.

CASE 2.—Mrs. N. C., 47 years of age, died on January 28, 1933, at 10:30 A.M. She was admitted to the hospital on January 26, 1933, with a diagnosis of bronchial asthma, and died suddenly at the completion of bronchoscopic lipiodol injection two days later. Bronchial asthma had begun in 1917. She had been treated by laryngologists with various surgical measures, and was readmitted on January 26, 1933, for the purpose of bronchoscopic examination and lipiodol injection which was done on January 28, 1933, for a possible bronchiectasis. She developed dyspnea, became unconscious in three minutes, and expired five or six minutes later.

CASE 3.—W. H. S., 50 years of age, died August 5, 1934, at 1:54 A.M. He had been admitted June 19, 1933, for a moderately severe asthma, especially severe during cold weather and changes in weather. He usually improved during hot weather. On July 25, 1934, his attacks became more frequent and he became weak. On August 4, he was markedly dyspneic.

CASE 4.—M. B., 54 years of age, died December 11, 1933. The patient was first seen on March 24, 1933. She had had asthma for 20 years or

more (seasonal variation, related to cold). There was asthma in the family. Adrenalin had been used daily. She had been severely ill for the previous month and during the last two days, adrenalin failed to give relief and only morphine was effective.*

CASE 5.—Mrs. A. R., 43 years of age, died November 16, 1936, at 2:53 A.M. She was admitted to the dispensary on January 25, 1933, with a history of illness dating from July, 1932, when a cold caused her to go to bed. She had wheezing. In November, 1932, the patient had another attack, lasting a month. She had pneumonia in 1926, hay fever for many years. She was admitted to the hospital on January 31, 1933. By March 7, she was moderately improved. By April 5, she was much improved. On January 14, 1936, she was readmitted, but had no real attacks of asthma. She coughed very much. On September 18, 1936, she was again seen in the dispensary; there was swelling of the entire body beginning in May, 1936. For a year previously she had had occasional morning nausea. On October 17, numerous skin lesions appeared on the forearms, thigh, and sacrum; these were diagnosed as circinate urticaria. On October 27, she had venous congestion, asthmatic wheezes. On November 13, erythematous areas broke out over the thighs and buttocks. At 10 P.M., on November 15 the patient suddenly became cyanotic and comatose. She expired on November 16.

CASE 6.—C. P., 61 years of age, died on January 20, 1939, at 3 P.M. He had suffered from asthma for nineteen years, and for the last five months had been almost constantly in a state corresponding to *status asthmaticus*. He had used large amounts of adrenalin. He had diabetes and cardiac involvement with fibrillation. On January 18, he became extremely exhausted, could not sleep, and was very thirsty. He was admitted to the hospital with a blood pressure of 110/76 mm. Hg, pulse 140, urinary output decreased. There was albumin in the urine and no sugar. There was no typical picture of shock. Typical picture of asthma in the lungs prevailed.

CASE 7.—J. L., 44 years of age, died February 27, 1939, at 9 P.M. He had developed a head cold ten days before admission. On February 24, he apparently had another head cold, and on the twenty-sixth was seen by this physician. By evening his condition was worse, and wheezing was present. On the morning of the twenty-seventh he had dyspnea. He died an hour after admission.

In all seven cases careful post-mortem examination revealed characteristic pulmonary changes, including obstructive plugs, mucus, hypertrophy of musculature, erosion, and eosinophilic infiltration.

When we examine the associated meteorological conditions with these deaths observed by Dr. Hilding, situations similar to those witnessed in the deaths reported by Vaughan become evident, though here the en-

*In Case 4, morphine was given during the last two days; in one of the cases codeine was given three hours before death, and in another, pantopon grain ½ and atropine 1/150 one-half hour before death. Vaughan and Graham[1] have called attention to the apparent frequency with which deaths in severe asthma follow the administration of opiates.

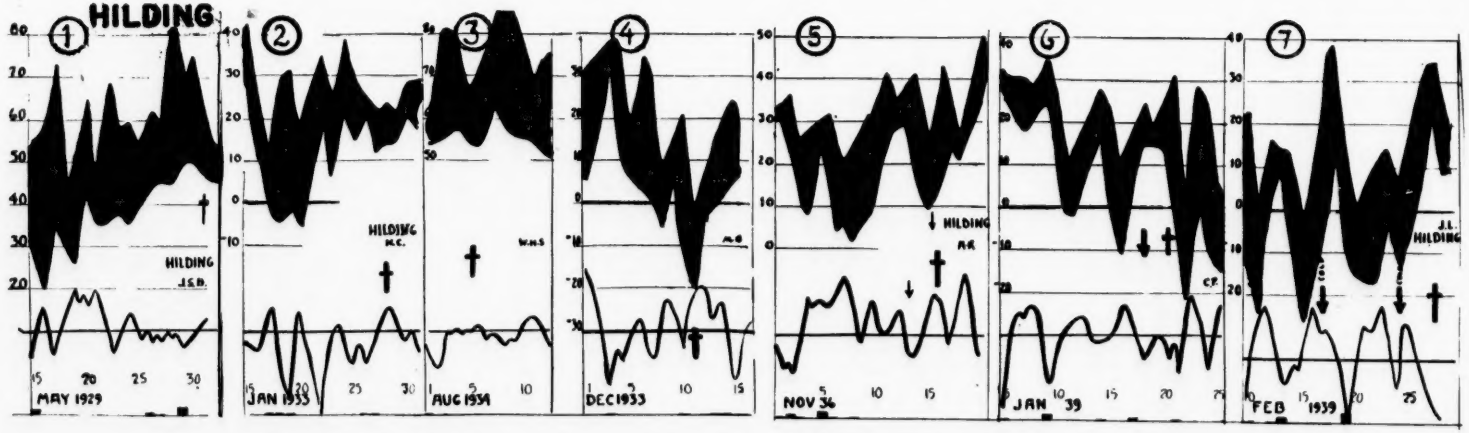

Fig. 3.—Meteorogram to illustrate asthmatic attacks and deaths in Cases 1 to 7 of Dr. Hilding.

vironmental forces are more brusque and severe, five of the seven patients dying in periods of unusual cold.

In Case 1, death occurred with a sharp decline in temperature from high levels. In Case 2, death occurred with a striking barometric crest and with temperature decline. In both Cases 1 and 2, it is very probable that the preceding period of organic change associated with the cold two weeks previously may have conditioned the patient.* In Case 3, death occurred with midsummer temperatures, but with a decline, and at a time of relative increase in barometric pressure. Case 4 died during a winter cold wave crest, with temperature of –20° F.; Case 5 with a late autumn cold wave, at the time of a barometric crest. Death occurred in Case 6 with a rapid rise in environmental temperature, after a decline to –10° F. and two days after the onset of the attack. There was considerable precipitation at the time. In Case 7, onset of the "cold" occurred immediately in the wake of a barometric crest, with wide swings in environmental temperature from –24° to 40° F. Accentuation of the "cold" came with the end of the next fall in temperature, and death with the passage of a succeeding tropical crest, with increased temperature and lowered barometric pressure.*

TABLE I

		TEMPERATURE ANTECEDENT TO ATTACK		TEMPERATURE AT TIME OF DEATH*	
		FALLING	RISING	FALLING	RISING
Vaughan Cases					
I, Episode No.	1.	x		x	
	2.	x			x
	3.	x			x
	4.	x			x
	5.	x			x
	6.	x		x	
	7.	x			x
	8.	x			x
II			x	x	
III			x	x	
V			x		x
VI		x			x
Hilding Cases					
I			x	x	
II		x		low	
III		x		low	
IV		x		x	
V		x		low	
VI			x		x
VII			x		x

*Or during period of subsequent recovery in Vaughan's Case I, episodes 1 to 7.

It will be seen in Table I that the weather change preceding an asthmatic attack is usually that of falling temperature and that exitus

*It is probable that the normal organism requires a period of approximately two weeks for recovery from any severe metabolic disturbance, such as that associated with the passage of a severe polar air mass.

occurs with subsequent rise of temperature. Thus in 13 of 19 episodes there is a definite fall in temperature before the attack. By the time death occurred, this had been reversed, and in 10 of the episodes, temperatures were already rising. However, as in Vaughan's Cases 2, 3, and 4, and Hilding's Cases 1, 6, and 7, other types of weather change may be significant (i.e., change in humidity, air ionization, wind velocity, etc.). *Marked changes*, and the body's physiological adjustments thereto, are the important factors.

Furthermore, as may be seen in some of the figures, and as undoubtedly obtained during periods not charted in the figures, there are similar changes in the life span of an asthmatic person which do not affect the patient seriously. However, if the combination of all factors (allergen exposure, fatigue, infection, constipation, etc.) is favorable to the development of an attack, the weather changes may become the determining factor.

There was a period of slightly over two weeks in June, 1943, when Richmond, Virginia experienced a temperature of at least 90° F. each day. This heat wave broke June 29, with heavy showers and a temperature fall of 30°. During the ensuing days the temperature ranged around 70° F. In the three days following June 29, ten mild asthmatic patients (some dust and pollen cases and some intrinsic bacterial asthmatic) reported to the office with severe exacerbations. None died. Some ambulant asthmatic patients were unaffected. Three severe cases, under treatment in hospital, did not become worse. Here, again, we observe the factor of "personal idiosyncrasy," which in this instance means physiologic status at that time.

DISCUSSION

To the passage of alternating tropical and polar air masses, i.e., the cyclonic circulation, the normal human organism constantly adjusts in wide autonomic excursions involving all organs and tissues. The passage of a polar air mass is associated with a sympathicotonia whereby the organism seeks to insulate itself. The blood from the periphery is relatively more alkaline at this time; then smooth muscle tone is increased, blood pressures rise, and a relative anoxia obtains in large regions of the periphery. A corrective reversal of the disturbed organbalance takes origin with the production of capillary-active substances in such regions of anoxia. As a result, the organism becomes more acid, blood pressure falls, the capillaries become more permeable, smooth muscle relaxes, the tissues become hydrated, etc. If coincidentally a tropical air mass passes, this phase of reversal may in time be accentuated, and tissue swelling, sharply falling blood pressure, etc., may reach stages that come to clinical consciousness, as, for instance, in the arthritic "weather prophet."

It must be obvious that with such organic pendulation (probably exaggerated in the allergic patient) one extreme state or the other will be

reflected with an accentuation of unfavorable symptomatology, and the other will be associated with the opposite state. Such pendulation, expressed in chemical balances such as a swing from a high to a low blood pH, from high to low K/Ca ratio, from high to low protein concentration, etc., involves, as already mentioned, every balance in the fluids and tissues.

Obviously, any number of factors can initiate or accentuate such pendulation. Weather change is one; emotion, infection, physical activity, digestive function, endocrine rhythm such as menstruation are others. The greater absorption of an allergen (due either to greater quantitative exposure or greater facility and speed in absorption) must play a role, and weather factors may be effective both in conditioning the allergic subject on the one hand and in changing the quantitative or qualitative state of the allergen to which the individual is sensitive.

It is evident that the asthmatic patient is at times extremely sensitive to such changes in the air mass. Nelson and his collaborators[4] have called attention to this, and Peters[5] in a recent paper insists that "among the non-specific causes of bronchial asthma, weather changes must be considered among the most important. A knowledge of the direction of the wind and the approach of bad weather can help us to understand the patient's present symptoms and often predict the degree of health he will enjoy during the following days.

"Anyone who will take the trouble to learn these facts will greatly profit from it. It is best to start by taking certain patients for study and recording their good and bad days. It will soon be learned that there are patients who, without their knowledge, exactly follow the barometric pressure.

"After a month or so, these patients can be used as indicators, and it will be learned that whenever they have symptoms, almost all the patients of their group will have symptoms. When these indicator patients are well, all other patients in this group will usually be well also."

It is also possible that with rather steady exposure to an allergen of low activity for the individual patient (house dust for example) weather change might cause an acute attack. From the allergic point of view this attack is associated with house dust sensitization, even though exposure to house dust does not cause continuous symptoms. Both factors may play a part.

Weather change may be and frequently is a factor in tipping the balance toward a fatal outcome. Morphine and other narcotics may be factors. It is conceivable that one might tolerate narcotic administration at times and not do so when the weather situation is unfavorable. Nedzel's[6] work has made evident that the minimal lethal dose for a variety of pharmacologic agents, including opiates, varies from day to day and primarily varies with the weather of the time.

CONCLUSION

The inference is obvious that the clinician, while properly interested in the allergic background of the clinical symptoms, should by no means neglect the other environmental forces which are of significance not only for the allergic patient but for other individuals as well. Recognition of the basic organic rhythm, with its periods of increased or decreased susceptibility to attacks, should, under all conditions, prove useful in the evaluation of the symptoms and therapy, as well as the prognosis.

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THE RELATIONSHIP OF BRONCHIAL ASTHMA (AND HAY FEVER) TO PULMONARY TUBERCULOSIS

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WIDE variance exists in prevoius reports regarding the frequency of the coexistence of pulmonary tuberculosis and bronchial asthma. A study of the literature also reveals great divergences of opinion concerning the significance of such an association. Some writers have maintained that the two conditions are mutually exclusive, while others support the diametrically opposite view that these two illnesses are always coexistent. Opinions most frequently expressed by previous writers may be roughly grouped as follows:

1. Asthma and pulmonary tuberculosis are antagonistic and therefore are rarely, if ever, found together.[1-5]

2. Asthma and tuberculosis may occur together, but their coexistence is purely coincidental and no causal relationship exists between the two.[6-8]

3. In all or in the vast majority of instances,[15] asthma is of tuberculous origin.[9-14] Views less frequently expressed include the following:

   (a) Asthma, at the outset, frequently starts as a result of an allergy to the tubercle bacillus (tuberculo-allergic asthma),[15, 16] but hypersensitiveness to other allergens may develop later.[17, 18]

   (b) Asthma predisposes to pulmonary tuberculosis.[19]

   (c) Asthma is favorably influenced by pulmonary tuberculosis.[40]

Statistics on the coincidence of bronchial asthma and tuberculosis have usually been obtained either by studying the incidence of tuberculosis among patients with bronchial asthma or by studying the incidence of bronchial asthma among patients under treatment for active pulmonary tuberculosis.[11, 12, 14, 19, 20-30, 35]

It is the intention of the writers to investigate both aspects of the question. In this communication, they will present their findings in patients hospitalized with active pulmonary tuberculosis. The results of the study on patients whose cardinal symptom is bronchial asthma will be reported in a subsequent communication.

In an early report, Schröder[31] found 30 cases with typical asthmatic symptoms among 4,716 patients with pulmonary tuberculosis, an incidence of 0.6 per cent. In a subsequent survey of 8,971 cases of pulmonary tuberculosis, he[32] found the same incidence. Similar reports on the infrequent association of the two diseases were cited by Schröder and include the following: Glai (0.8 per cent); Hochstetter (0.67 per

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cent); Klewitz (1.9 per cent); and Sedillot (0.25 per cent), the latter finding only 12 cases of asthma among 4,600 individuals with tuberculosis. Küpper[33] found, among 1,000 patients with tuberculosis, only 14 (1.4 per cent) with true bronchial asthma. In all except one of these, the asthma preceded the tuberculosis. Lichtenstein[34] reported an annual incidence of 10 cases of moderate or severe asthma among 1,000 tuberculous patients in residence in the Chicago Municipal Sanatorium, an incidence of about 1.0 per cent. Bray[36] stated that only one of 200 patients with active tuberculosis suffered with true bronchial asthma.

In contrast to the above conservative estimates, were the reports of workers who found a much more frequent association of the two diseases.[9-14, 28, 35] Some of the early workers maintained that a majority of cases of asthma were tuberculous in origin.

The failure to differentiate between true bronchial asthma and asthmatoid symptoms caused by intrapulmonary pathology was undoubtedly responsible for the wide variations in the findings of the early investigators. Tuberculous mediastinal lymph nodes, chronic bronchitis, pulmonary emphysema, bronchiectasis, displacement of the mediastinum and trachea, neoplasm, foreign bodies, and particularly tracheobronchial tuberculosis may produce asthmalike symptoms. Before the era of the roentgen rays, the underlying pulmonary pathology was frequently missed, so that conditions causing asthmatoid symptoms were commonly diagnosed as bronchial asthma. Today, this problem in differential diagnosis is partly solved by the application of more modern criteria for the diagnosis of asthma, such as a positive family or personal history of atopy (hereditary type of allergy), positive cutaneous reactions to skin tests with common allergens, an excess of eosinophiles in the sputum, a favorable clinical response to epinephrine, and a characteristic symptomatology and clinical course.

Despite these diagnostic aids, it is often difficult, in cases of pulmonary tuberculosis, to make the differential diagnosis between bronchial asthma and asthmatoid breathing resulting from tuberculous pathology. It is possible for patients with tuberculous involvement of the tracheobronchial passages to have true bronchial asthma as well. The two conditions may be present simultaneously or may occur independently.

The writers, therefore, considered it advisable, in their studies, to investigate as many patients as possible by means of the differential criteria upon which the diagnosis of bronchial asthma could be made. The fact that bronchial asthma is now generally accepted to be an atopic illness, based upon an hereditary predisposition, proved of considerable assistance in the differential diagnosis in many doubtful cases. In this investigation on tuberculous patients, every effort was made not only to determine the presence of bronchial asthma, but also to uncover a past or present history of other characteristic atopic illnesses, including hay fever, angoineurotic edema, urticaria, chronic infantile eczema, migraine, food and drug hypersensitivities, etc. Particular attention

was paid to a history of hay fever, since this condition is a characteristic manifestation of atopy less likely to be confused with other nonatopic conditions than most of the other atopic illnesses. Hay fever, which is based on a pollen allergy, occurs in this locality about as frequently as asthma and is an equally reliable index of the presence of the atopic state.

In the attempt to detect and establish the presence of atopy among tuberculous patients, the following steps were taken: Each patient was carefully questioned concerning a past or present history of atopic illnesses in himself or in the immediate members of his family. Patients with suggestive histories of atopy were often requestioned by another examiner at a later date in order to check the data and to obtain a second opinion as to the diagnosis. In a patient with a definite or suggestive personal or family history of asthma or of other atopic illnesses, intracutaneous tests were performed with the inhalant and food allergens which are the most common offenders in bronchial asthma. Blood examinations and sputum studies for eosinophiles in excess were made on doubtful cases. In every patient, the chest findings were checked, not only for the pulmonary tuberculous lesion, but also for the asthma.

In this manner, a total of 386 patients on the adult wards of Sea View Hospital in New York City were studied during the years of 1939 and 1940. The series included 250 females and 136 males.

THE INCIDENCE OF ASTHMA AMONG PATIENTS WITH PULMONARY TUBERCULOSIS

Females.—Among the 250 females studied, a diagnosis of bronchial asthma could definitely be made in eight patients, an incidence of 3.2 per cent (Table I). In five of the eight patients, the family history of atopy was definitely positive, and in one it was doubtful. In five subjects, the diagnosis of asthma antedated the recognition of the tuberculosis by from 6 to 16 years. In two cases, no definite precedence in the date of onset could be determined. In only one patient (M. C.) was the diagnosis of tuberculosis made before the asthma developed, the interval being six years.

In one patient (A. W.), caseous mediastinal lymph nodes ruptured into the trachea. Granulomatous caseous material was found in the trachea on the first bronchoscopic examination on June 1, 1938. These findings had disappeared by the time another bronchoscopic examination was made on Aug. 18, 1938. Despite the improvement in the bronchoscopic picture, the asthmatic attacks persisted. This patient manifested only doubtful cutaneous reactions and had an indefinite family history of atopy. However, she had a blood eosinophile count of 5 per cent, and the clinical course appeared to be that of an atopic type of bronchial asthma. She was, therefore, included among the asthmatic cases.

Definite positive cutaneous reactions to foods and inhalants were obtained in six of the eight cases with bronchial asthma. In two, the reactions were doubtful. The degree of the reactions varied from one-plus to four-plus. For the most part, the reactions were relatively weak for reasons which will be discussed later. Hay fever was associated with asthma in only one patient (M. G.).

Males.—Among 136 male patients with tuberculosis, definite bronchial asthma was found in four, an incidence of 2.9 per cent (Table I). The ages of these four patients ranged from 25 to 59 years. The family history was positive for atopy in only one of these.

In one case, asthma antedated the recognition of tuberculosis by 14 years, and in another case by 3 years. In one case, no precedence in time of onset could be determined; in another, tuberculosis antedated asthma by 5 years. Hay fever was associated with the asthma in one instance (R. B.).

THE INCIDENCE OF HAY FEVER AMONG PATIENTS WITH PULMONARY TUBERCULOSIS

Females.—In the group of 250 females, a history of hay fever was obtained in 10, an incidence of 4 per cent (Table II). The ages of the affected patients ranged from 17 to 37 years. One of these patients (M. G.) also had asthma. Seven patients were clinically sensitive to ragweed and four to grass pollens. One patient, who had lived in the West, gave a history of previous sensitivity to sage brush and purple daisy. A positive family history for atopy was reported in only four of the ten cases.

According to the histories given, the hay fever antedated the diagnosis of tuberculosis in four instances by from 2 to 9 years. In three cases, the tuberculosis preceded the onset of hay fever by from 2 to 9 years. In three cases, no definite precedence could be established, the ages of onset being within one year of each other.

Males.—The only case of hay fever encountered among the males was in the asthmatic patient (R. B.) already mentioned (Tables I and II). The incidence of hay fever in the series of males was, therefore, only 0.8 per cent.

THE INCIDENCE OF ATOPIC NONCLINICAL CASES AMONG PATIENTS WITH PULMONARY TUBERCULOSIS

Among the 250 female patients studied, there were 8 (3.2 per cent) with positive atopic family histories who presented no clinical symptoms of atopy.

Among the 136 males, there were 6 (4.4 per cent) such cases (Table III).

These patients generally presented doubtful or negative cutaneous reactions to various allergens. An increase in blood eosinophiles was frequently noted in this group of cases. Such clinical findings are com-

TABLE I

CASES WITH BRONCHIAL ASTHMA AMONG PATIENTS WITH PULMONARY TUBERCULOSIS

NAME	AGE	SEX	RACE	ATOPIC FAMILY HISTORY	AGE AT OUTSET OF		PULMONARY LESION	POSITIVE SKIN REACTION	GENERAL REMARKS
					ASTHMA	TBC.			
K. W.	33	F.	W.	+	15	26	Cas. pn. tbc., R.U.L. Exud. prod. tbc., L.U.L.	House dust Wool	
B. M.	30	F.	W.	+	15	21	Caseous pneumonic tuberculosis, R.U.L.	House dust Ragweed Corn Almond	At age of 15 years—wheezing and heaviness on chest during common colds Severe attacks of asthma since age of 28
A. F.	58	F.	W.	–	43	57	Cas. pn. tbc., R.U.L. Exud. tbc., left lung	House dust Wheat Corn Green pea Rice Flaxseed	Urticaria after ingestion of berries and shellfish Asthma improved with onset of tuberculosis
S. J.	45	F.	W.	+	37	37	Bilateral cas. pn. tbc.	House dust Horse ep. Egg Cabbage	Asthma improved when the tuberculosis became aggravated at age of 40
M. G.	25	F.	W.	+	8	17	Caseous pneumonic tuberculosis, R.U.L.	Ragweed Timothy House dust Silk Corn Goat ep.	Asthma was worse in 1936 and 1937, when the tuberculosis improved In 1938 and 1939, with progression of the pulmonary lesion, the asthma improved Hay fever since age of 19
A. W.	23	F.	C.	+?	22	23	Bilateral pulmonary tbc. Cas. pn. in rt. Exud. prod. in left lung Tuberculous tracheobronchitis Rupture of paratracheal caseous node into trachea		Bronchoscopy, in 6/1/38, showed tuberculous granuloma in trachea—which was absent on bronchoscopy on 8/18/38 Asthmatic attacks continued Blood eosinophilia of 5 per cent

M. C.	28	F.	W.	+	25	19	Bilateral cas. pn. tbc.	House dust Timothy Ragweed	Atelectasis of R.L.L. due to tuberculous bronchitis with obstruction of R.L.L. bronchus
M. R.	19	F.	W.	–	6	16	Cas. pn. tbc.		Sputum showed 14 per cent eosinophiles
A. G.	56	M.	W.	–	30	33	Bilateral cas. pn. tbc. with emphysema	Negative	Tuberculosis was diagnosed on basis of x-ray in 1914 (aged 30) Sputum negative for tbc. up to 1936
R. B.	25	M.	W.	–	21	24	Bilateral cas. pn. tbc.	House dust Wheat Ragweed Timothy Chicken ep.	Has hay fever simultaneously with asthma
A. B.	34	M.	W.	+	15	29	Bilateral cas. pn. tbc.	House dust Chicken ep. Wheat	
W. D.	59	M.	W.	–	56	51	Bilateral cas. pn. tbc.	House dust Chicken ep. Ragweed	Blood eosinophilia 9 to 11 per cent

Abbreviations used in Tables I and II:

Tbc., Tuberculosis; Cas. pn. tbc., Caseous pneumonic tuberculosis; Exud. prod., Exudative productive; Exud. tbc., Exudative tuberculosis; R. U. L., Right upper lobe; R. L. L., Right lower lobe; L. U. L., Left upper lobe; H. F., Hay fever; Ep., Epithelium.

TABLE II

CASES WITH HAY FEVER AMONG PATIENTS WITH PULMONARY TUBERCULOSIS

NAME	AGE	SEX	RACE	ATOPIC FAMILY HISTORY	AGE AT OUTSET OF		PULMONARY LESION	POSITIVE SKIN REACTION	GENERAL REMARKS
					H. F.*	TBC.			
V. J.	26	F.	C.	+	19	21	Caseous pneumonic tuberculosis, R.U.L.	Ragweed	
A. H.	20	F.	W.	+	19	19	Productive-infiltrative tuberculosis	Timothy Tomato Pork	Urticaria
M. S.	34	F.	W.	–	32	23	Bilateral cas. pn. tbc.	Ragweed Timothy Plantain	
T. E.	29	F.	W.	–	26	29	Caseous pneumonic tuberculosis	Ragweed	
B. R.	17	F.	C.	–	14	13	Bilateral cas. pn. tbc.	Ragweed	3 per cent eosinophiles
O. M.	32	F.	W.	+	20	29	Bilateral cas. pn. tbc.	Sage brush Purple daisy	4 per cent eosinophiles
T. E.	32	F.	W.	–	22	21	Bilateral cas. pn. tbc.	Timothy Ragweed	
L. N.	36	F.	W.	–	34	32	Caseous pneumonic tuberculosis	Ragweed	
E. G.	37	F.	C.	–	27	24	Cas. pn. tbc., R.U.L. Bilateral hematogenous dissemin.	Timothy	
M. G.	25	F.	W.	+	9	17	Caseous pneumonic tuberculosis, R.U.L.	House dust Silk Corn Goat ep.	Asthma began at age of 8 This case also included in Table I
R. B.	25	M.	W.	–	21	24	Bilateral caseous pneumonic tuberculosis	House dust Wheat Ragweed Timothy Chicken ep.	Asthma simultaneous with hay fever This case also in Table I

*See Table I for meaning of abbreviations.

mon among members of atopic families and suggest that these individuals are potential subjects of atopic disturbances. It was not possible, in this study, to determine whether the presence of an active tuberculosis had been a contributory factor in suppressing the atopic manifestations in these patients.

Summary of Findings.—Analyzing the results for the entire series, one finds that among 386 male and female patients with tuberculosis, there were 12 with a past or present history of bronchial asthma, an incidence of 3.1 per cent (Table IV). A history of hay fever occurred in 11 patients, or 2.8 per cent of the series. In addition to the above patients, 3.6 per cent of the series gave suggestive family histories of atopy or manifested doubtful cutaneous reactions or increased eosinophile counts, but lacked any clinical symptoms of atopy.

Results of Intracutaneous Testing.—The patients in this series showed positive skin reactions to the same allergens found to be common offenders among nontuberculous atopic patients. The positive reactions, however, developed slowly and weakly, following injections. Testing materials in the dilutions routinely employed for diagnostic purposes among allergic patients produced negative or doubtful reactions in most of the tuberculous cases. Stronger extracts elicited definitely positive but weak reactions. The wheals appeared slowly with borders which usually could neither be palpated nor clearly visualized. In most instances, only a faint and narrow band of erythema surrounded the wheals, and frequently this component of the reaction was entirely absent. Often there was little or no pruritus associated with the whealing. The positive reactions resembled those elicited in the testing of aged patients.

This poor response of the skin to tests with allergens was, in all probability, the result of the debilitating effects of the tuberculosis. That it was not caused by an impairment of antibody production in the tuberculous patient was demonstrated in another study by the writers, in which it was found that tuberculous patients, artificially sensitized to *Ascaris lumbricoides* extract, responded actively in the formation of skin-sensitizing antibodies (atopic reagins) to this antigen.

DISCUSSION

The incidence of asthma among the 386 patients of both sexes at Sea View Hospital was 3.1 per cent. This approximates the reported incidence of asthma among the rest of the population. Vaughan[38] (1934) made a survey of an entire Virginia community comprising 508 individuals and found a present or past history of asthma in 3.3 per cent. Rowe,[43] in an analysis of the histories of 1,600 university students in California, found a past or present history of asthma in 3 per cent. In a survey of 3,141 individuals in the city of Colorado Springs, Service[37] reported the incidence of asthma to be 3.6 per cent. No recent surveys have been made of the incidence of asthma in New York City, but there is little to indicate that it deviates appreciably from

the averages of the above-mentioned communities. Under the circumstances, the finding of 3.1 per cent of asthmatic patients among the adult population of Sea View Hospital may be considered to be within normal limits. It is a complete refutation of the assertations that asthma and tuberculosis are mutually exclusive or that their association is rare.

TABLE III

NONCLINICAL ATOPIC CASES AMONG PATIENTS WITH PULMONARY TUBERCULOSIS

NAME	AGE	RACE	SEX	ATOPIC FAMILY HISTORY	SKIN REACTIONS	BLOOD EOSINOPHILIA
L. B.	25	C.	F.	Doubtful	doubtful	
A. R.	43	W.	F.	Son has hay fever	doubtful	3 per cent
R. T.	26	W.	F.	Aunt and brother have hay fever	negative	3 per cent
E. J.	39	W.	F.	Cousin has hay fever, asthma urticaria	doubtful	3 per cent
O. H.	51	W.	F.	Mother and brother have asthma	doubtful	2 per cent
O. P.	26	W.	F.	Brother has hay fever	negative	1 per cent
E. B.	24	W.	F.	Brother has asthma	positive	2 per cent
R. O.	22	W.	F.	Mother and sister have asthma	negative	
H. H.	19	W.	M.	Father has hay fever	positive	12 per cent
L. H.	27	W.	M.	Brother has asthma	positive	2 per cent
J. S.	20	W.	M.	Cousin has asthma	doubtful	1 per cent
S. R.	23	W.	M.	Cousin has asthma	positive	
H. H.	45	W.	M.	Doubtful	positive	4 per cent
E. M.	38		M.	Father had asthma	negative	4 per cent

TABLE IV

SUMMARY OF ATOPIC FINDINGS IN 386 CASES WITH PULMONARY TUBERCULOSIS

		NUMBER INVESTIGATED	ASTHMA		HAY FEVER		ATOPIC NONCLINICAL	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
FEMALE	White	179	7		7		7	
	Colored	71	1		3		1	
	Total	250	8	3.2	10	4.0	8	3.2
MALE	White	120	4		1		6	
	Colored	16	0		0		0	
	Total	136	4	2.9	1	0.8	6	4.4
	TOTAL	386	12	3.1	11	2.8	14	3.6

No evidence, moreover, was uncovered in the present study to support the view that tuberculosis predisposes to asthma. On the contrary, the data obtained on tuberculous patients with hay fever point to the opposite conclusion. It is generally agreed that hay fever is one of the major predisposing causes of asthma in this country. Furthermore, it has been estimated that, in patients with untreated hay fever, at least one-third may be expected to develop asthma as a complication. In the group at Sea View Hospital, however, only 2 of 11 patients with hay fever, or 18 per cent, had an associated or past history of asthma. This constitutes significant evidence that tuberculosis does not predispose to asthma for, if such were the case, the incidence

of asthma among hay fever patients with tuberculosis would have been greater instead of less than anticipated.

Also of significance in this study was the finding that, in 7 of the 12 cases of bronchial asthma, this illness preceded the diagnosis of tuberculosis by from 2 to 16 years. In only one instance did the tuberculosis seem to antedate the asthma. Hence, the hypothesis of some earlier clinicians[9-16] that the tubercle bacillus is the etiologic agent of asthma was not supported by our findings.

Nothing was found in the present study to support the theory that there is a special form of asthma among the tuberculous. The cases of bronchial asthma in this series were found to be sensitive to the common allergens, and their clinical behavior, from the point of view of asthma, did not differ from that in nontuberculous asthmatic patients.

Effect of Tuberculosis on Asthma.—The fact that asthma may be favorably influenced by tuberculosis was noted many years ago by Hoffman[40] and apparently finds corroboration in the present investigation. In most of the cases in which asthma antedated tuberculosis, there was an improvement in the asthmatic symptoms with the onset of tuberculosis. Conversely, with improvement or healing of the tuberculous lesion, the asthma tended to become more acute. It seems likely that the infective process in tuberculosis produces nonspecific ameliorative effects on the asthma similar to those commonly produced by other intercurrent infections.

Effect of asthma on tuberculosis.—The effect of asthma on the tuberculous process is not a favorable one. This view has previously been expressed by Hamann[35] and Lueg.[41] Asthmatic paroxysms in the tuberculous patient may constitute a real danger for, with the intense cough and increased secretion associated with the attacks, bronchogenic spread from an active caseo-pneumonic focus is facilitated.

In patients receiving therapeutic pneumothorax, paroxysms of asthma are particularly troublesome, because, during an asthmatic attack, there is a sharp rise in both the intrapleural and intrapulmonary pressures. The significance of this fact was recently brought out by Vaccarezza and Cucchiani Acevedo[42] in studies on asthmatic patients receiving pneumothorax. They noted not only a sharp increase in intrapleural pressure with the attack, but also observed an expansion of the lung and a reopening of the cavities in one case with bilateral pneumothorax. Although these changes are only temporary, they may seriously interfere with the effectiveness of the pneumothorax.

SUMMARY

1. Among 386 patients with active pulmonary tuberculosis at Sea View Hospital, 12 or 3.1 per cent presented a past or present history of bronchial asthma, and 11 or 2.8 per cent, a history of hay fever. These figures approximate the incidence of these illnesses in the normal population.

2. Of the 11 cases with hay fever, only 2 or 18 per cent gave a history of asthma; this did not exceed the anticipated incidence.

3. These findings refute the reports of earlier writers that: (a) tuberculosis and asthma are mutually exclusive, (b) tuberculosis predisposes to asthma, and (c) there is a common, specific form of asthma based on an allergy to tubercle bacillus.

4. In patients with pulmonary tuberculosis, a careful differential diagnosis must be made between true bronchial asthma and asthmatoid symptoms caused by organic bronchopulmonary pathology.

5. The allergens producing bronchial asthma in patients with tuberculosis are the same as those producing asthma among the nontuberculous. The effectiveness of skin testing with these allergens, however, may be impaired as a result of diminished cutaneous reactivity in such cases.

6. Asthmatic symptoms tend to improve with activity of a tuberculous process and to recur with the healing of the infection.

7. Asthmatic seizures are a potential source of danger to the favorable course of tuberculosis.

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AN ASSOCIATION BETWEEN RED-GREEN COLOR BLINDNESS AND SOME CASES OF ASTHMA AND HAY FEVER

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THE fact that the incidence of asthma and hay fever is about twice as great in boys as in girls suggests that one of the hereditary factors upon which some cases of asthma and hay fever depend, in part, is transmitted as a sex-linked recessive factor. The data of different investigators on the sex incidence of asthma, with age at onset of symptoms, have been analyzed by Wiener, Zieve, and Fries.[6] In 943 cases of asthma with onset of symptoms before the tenth year of age there were 627 males and only 316 females. On the other hand, no significant difference was found in the sex incidence of asthma in 1244 cases in which the first symptoms of asthma appeared after the age of 10 years. So far as hay fever is concerned, Nelson's[4] data on 856 cases indicate that the sex incidence of hay fever varies with age at onset of symptoms in the same way as that just described for asthma.

There is no direct method for determining whether some cases of asthma and hay fever depend in part on a sex-linked recessive factor. Csik and Mather[1] have, however, described a simple statistical technique for showing whether the excess of males affected with a certain condition does, or does not, depend on a sex-linked recessive factor. This technique is based on the assumption that "if sex-linkage is in fact the cause of the excess of affected boys, the excess should be confined to the sibs of the affected boys and fail to appear among the sibs of the affected girls." There is no question about the validity of this assumption for such a condition as red-green color blindness which invariably depends on a sex-linked recessive factor; but there is a question about its validity for conditions such as asthma and hay fever in which it has been assumed that some, but not all, cases depend in part on a sex-linked recessive factor. Csik and Mather analyzed the data of Zieve, Wiener, and Fries[7] on 90 allergic children, of which 28 were girls and 62 were boys. An excess of affected males was found among the siblings of the affected girls as well as among the siblings of the affected boys, but the excess of affected males was much smaller among the siblings of the affected girls than among those of the affected boys. Since the excess of affected males was not confined entirely to the siblings of the affected boys, Csik and Mather concluded that there was "no strong evidence for sex-linkage." One could, however, conclude from these same data not only that some cases of asthma and hay fever in boys probably depend in part on a sex-linked recessive factor, but that the

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hereditary basis of asthma and hay fever is probably more complex than that of the red-green color blindness.

Since the problem of the excess of boys affected with asthma or hay fever could not be solved directly, it was approached indirectly with what tools were then available. It was thought that if some cases of asthma and hay fever in boys depend in part on a sex-linked recessive factor, then there might be a relationship between those cases and other conditions, such as red-green color blindness, which are known to be dependent, in all instances, on a sex-linked recessive factor. If the incidence of red-green color blindness in boys with asthma or hay fever were found to be significantly greater than among unselected males, then that finding would be taken as indirect, but adequate, evidence that some cases of asthma and hay fever depend in part on a sex-linked recessive factor. Despite the fact that the use of red-green color blindness as just described has some disadvantages which will be discussed later, red-green color blindness was selected as the condition to be investigated, because it occurs quite frequently and its incidence in the general population is fairly well established.

PROCEDURE

The incidence of red-green color blindness in a group of 357 allergic male patients has been determined by means of the Ishihara tests for color blindness.[2] These patients were seen and tested in the Anaphylaxis Clinic of the Massachusetts General Hospital.* Each patient, or a responsible relative, was questioned regarding the age at the onset of the allergic symptoms and also the type of symptoms first experienced. All the patients had had or were having symptoms of either hay fever or asthma, or both. Those patients who were having or had had both types of symptoms were classified as hay fever or asthmatic patients according to which type of symptom was first experienced.

The Ishihara tests were administered, and the responses to them were interpreted according to the rules and criteria established by Ishihara. If the data obtained with the Ishihara tests are interpreted in terms of Ishihara's criteria, then the incidence of red-green color blindness among unselected males as determined by these tests is about 4 per cent. Out of 1286 male students tested by Miles[3] at Stanford University, 52 were red-green color blind according to Ishihara's criteria. This incidence of about 4 per cent, which corresponds quite closely with the findings of earlier investigators by means of other tests,[6] has been used as the basis of comparison for the findings made in the hay fever and asthmatic patients.

RESULTS

The main results of the present investigation are shown in Table I. The patients have been divided into four groups according to whether

*I wish to express my gratitude to Dr. F. M. Rackemann for placing the facilities of the Anaphylaxis Clinic at my disposal for this investigation.

the allergic symptoms began before or after the age of 13 years, and whether asthma or hay fever was first experienced. Of the 357 asthmatic and hay fever patients tested, 30 were found to be red-green color blind. This incidence of 8.4 per cent in the whole group is about twice as great as that among unselected males. This finding is statistically significant, the probability of its having occurred by chance being less than .01.*

An inspection of Table I will show furthermore that the incidence of red-green color blindness was highest among those patients whose first allergic symptom was asthma and was first experienced before the age of 13 years. Of these 104 patients, 13 were red-green color blind. This incidence of 12.5 per cent is about three times as great as that among unselected males. This finding is also statistically significant, the probability of its having occurred by chance being less than .01.

TABLE I

INCIDENCE OF RED-GREEN COLOR BLINDNESS AMONG 357 ALLERGIC MALE PATIENTS

TYPE OF PATIENTS	NO. OF PATIENTS	NO. RED-GREEN COLOR BLIND	PER CENT RED-GREEN COLOR BLIND
Asthmatic patients with onset of symptoms before 13 years of age	104	13	12.5
Asthmatic patients with onset of symptoms after 13 years of age	61	2	3.3
Total asthmatic patients	165	15	9.1
Hay fever patients with onset of symptoms before 13 years of age	85	7	8.2
Hay fever patients with onset of symptoms after 13 years of age	107	8	7.5
Total hay fever patients	192	15	7.8
Total allergic patients	357	30	8.4

The difference in the incidence of red-green color blindness in the two groups of hay fever patients is not significant. Therefore, all the hay fever patients have been handled as one group in order to simplify the statistical analysis of the data on them. Although the incidence of red-green color blindness among all the hay fever patients is somewhat lower than that among those asthmatic patients whose symptoms began before the age of 13 years, still the difference is not statistically significant. On the other hand, in comparison with unselected males, the increased incidence of red-green color blindness among all the hay fever patients is statistically significant, the probability of its having occurred by chance being .02. This statistical analysis shows that with respect to the incidence of red-green color blindness, all the hay fever patients fall in the same category as that occupied by those asthmatic patients whose symptoms began before the age of 13 years. Therefore, the findings so far described show that there is a relationship between red-green color blindness and some cases of asthma and hay fever.

In apparent contrast with the above patients are the 61 asthmatic patients whose symptoms began after the age of 13 years. Only two red-

*"p" was derived in this study by the method of Chi square.

green color blind individuals were found among those patients. Unfortunately, such a small number makes any statistical analysis of the data on these patients impracticable. Nothing further can be said about the apparent difference in the incidence of red-green color blindness in the two groups of asthmatic patients until further data are available on those patients whose asthma begins after the age of 13 years.

DISCUSSION

The relationship found between red-green color blindness and some cases of asthma and hay fever indicates that some cases of asthma and hay fever in boys probably depend in part on a sex-linked recessive factor. It should be noted, however, that the increased incidence of red-green color blindness found in the allergic patients does not account entirely for the greater incidence of asthma and hay fever in boys than in girls. This failure is probably due to the fact that red-green color blindness probably depends on at least two different factors, one of which is probably not a sex-linked recessive factor. If this were the case, tests for red-green color blindness would not detect the presence of the R-G sex-linked recessive factor, that is, the sex-linked recessive factor upon which red-green color blindness depends when that factor did not occur with the nonsex-linked factor upon which red-green color blindness also depends. Consequently a direct test for the R-G sex-linked recessive factor would probably show a greater degree of association between that factor and asthma and hay fever than the Ishihara tests have shown between those allergic conditions and red-green color blindness. Unfortunately the nature of this factor is not as yet known. Further knowledge about this factor, and especially a direct test for it, would probably show just how many cases of asthma and hay fever depend in part on a sex-linked recessive factor. Furthermore, such knowledge and such a test would probably reveal the nature of the hereditary basis of the relationship between red-green color blindness and some cases of asthma and hay fever. For the present, the following two formulations might be considered as alternative working hypotheses: On the one hand, the relationship found between red-green color blindness and some cases of asthma and hay fever may indicate that those cases depend in part on a sex-linked recessive factor that is closely linked with the R-G sex-linked recessive factor; on the other hand, this relationship may indicate that those cases depend in part on the R-G sex-linked recessive factor itself.

SUMMARY

1. One hundred sixty-five asthmatic male patients and 192 hay fever male patients have been tested for red-green color blindness by means of the Ishihara tests.

2. The incidence of red-green color blindness in the whole group of patients was 8.4 per cent, which is about twice as great as the incidence

of about 4 per cent among unselected males. This difference is statistically highly significant.

3. The relationship thus found between red-green color blindness and some cases of asthma and hay fever indicates that some cases of asthma and hay fever in boys probably depend in part on a sex-linked recessive factor.

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POLLEN STUDIES OF THE PHOENIX AREA

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FIRST reports on the hay fever problem in southern Arizona were made by Watson and Kibler[1] in 1922. Since that time, additional data dealing chiefly with central Arizona have been published by Phillips[2] and others. These studies have not included graphs of pollen concentration in the atmosphere, and it is for this reason that the present work may be of value and may constitute an addition, and in a large measure, confirmation of the conclusions previously drawn by these authors. Lamson's[3] study of northern Arizona was made in connection with work done on the California desert areas which are similar in many respects to our Arizona desert.

The outstanding feature of the climate of this region is the low humidity and lack of rainfall. The annual precipitation averages about 8 inches. The average mean relative humidity is 38 per cent saturation. This is approximately half of what it is in the Middle West. This lack of moisture allows pollen grains to remain in the air for many days and probably weeks. At midday the heat of the sun striking the earth carries the dust particles away from the earth's surface, and the cool nights bring this blanket of dust and pollen back down. This partially explains the fact that symptoms of pollen allergy are aggravated at night and in early morning. The average air motion of 5 miles per hour scatters the largest portion of the dust cloud, so that the dust movements are not quite as vertical as the preceding statement might indicate. As a matter of fact, many pollen grains are carried miles out on the desert, and only a few of them find their way back. We have found occasional pine pollen grains when the nearest pine pollinating was 50 miles away.

The dry river bottom, 2 miles across in places, with a subsoil current of water, grows vegetation which contributes particularly cottonwood, Russian thistle, salt bush, and some of the rarer shrubs.

In spite of these facts, the total pollen counts, as may be seen in the charts, are very much lower at all seasons than are found at the peak of the ragweed season of the Middle West, where the ragweed counts go as high as 4000 per cubic yard. The total pollen count here according to our studies seldom runs over 30 per cubic yard. Weeds do not thrive except when irrigated, and when land is not being utilized and cultivated here it is not watered. Therefore, vacant lots and roadsides are quite free of vegetation. Although canal banks produce an abundance of Johnson grass, this is usually cut or burned off several times

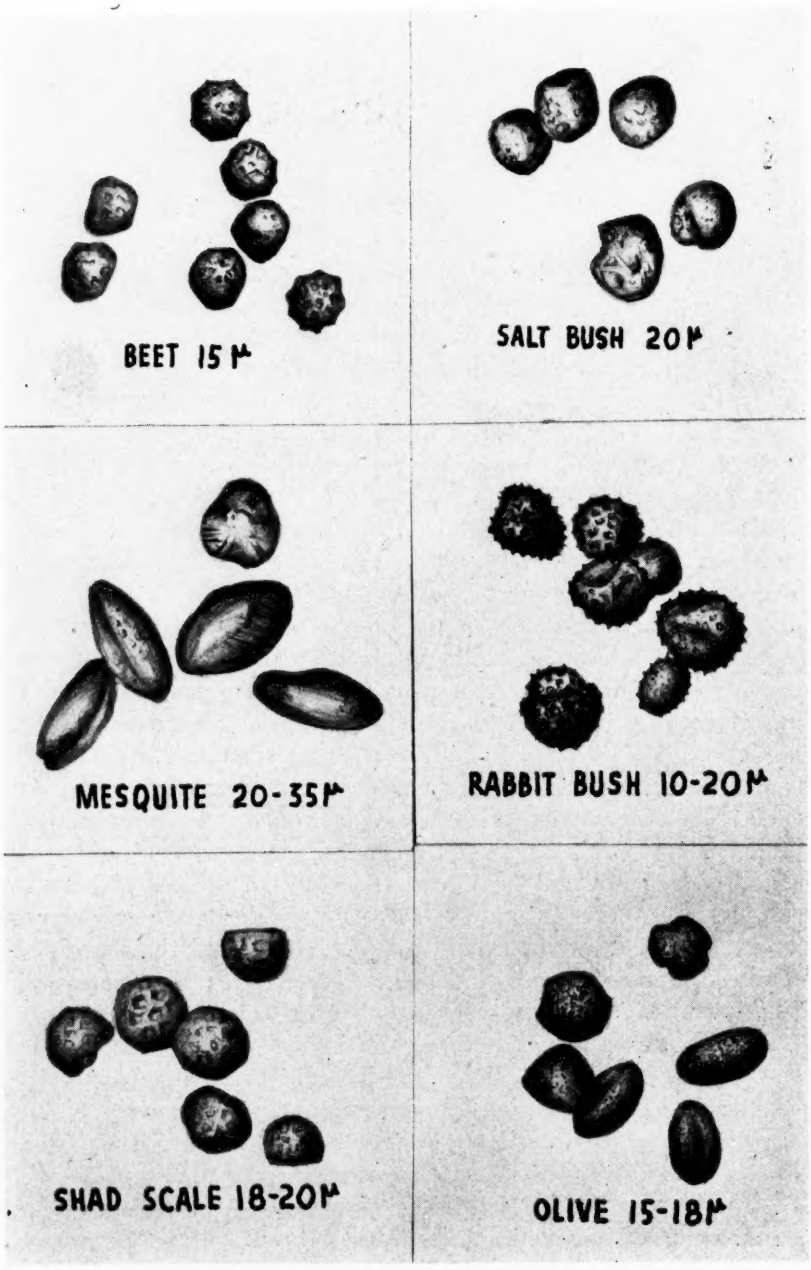
BEET 15 μ
SALT BUSH 20 μ
MESQUITE 20-35 μ
RABBIT BUSH 10-20 μ
SHAD SCALE 18-20 μ
OLIVE 15-18 μ

Fig. 1.

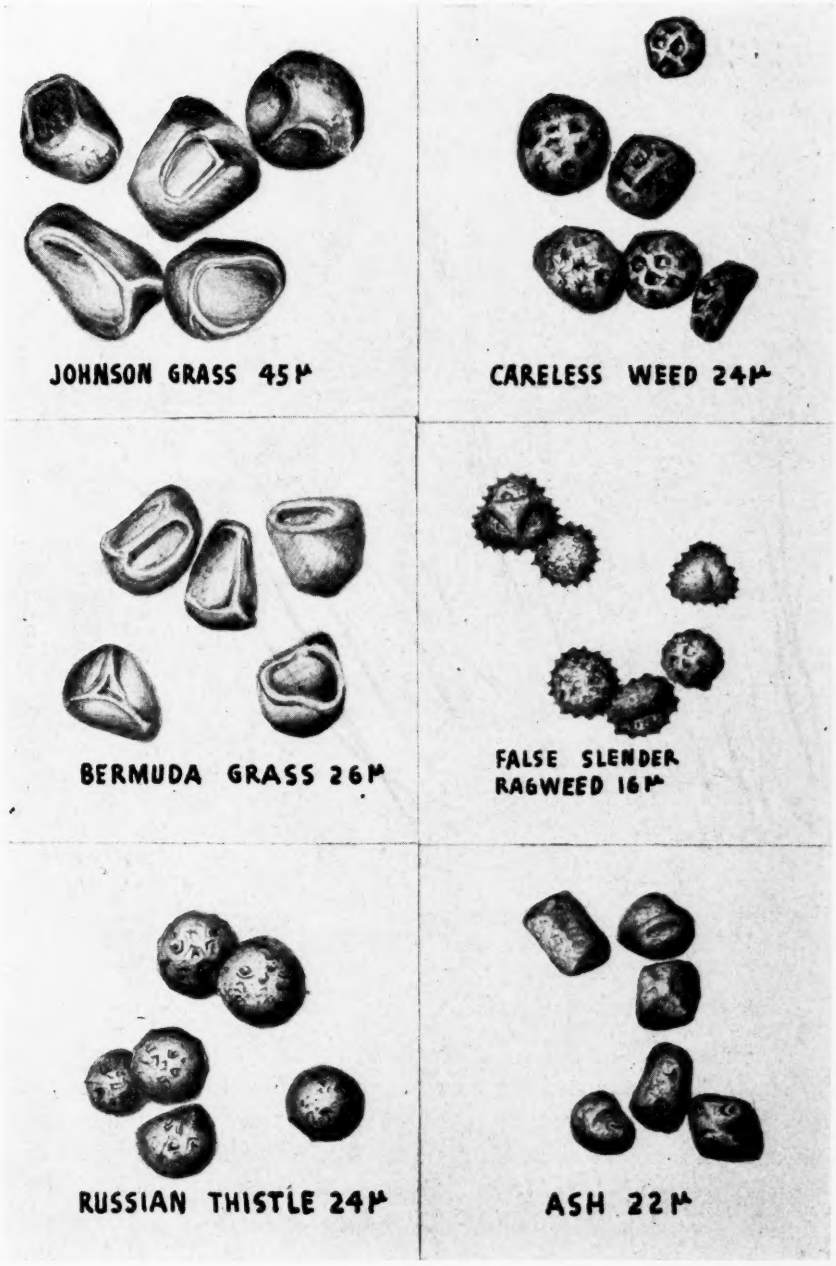
JOHNSON GRASS 45μ
CARELESS WEED 24μ
BERMUDA GRASS 26μ
FALSE SLENDER RAGWEED 16μ
RUSSIAN THISTLE 24μ
ASH 22μ

Fig. 2.

during the summer. The Bermuda grass is practically the only grass used in lawns, and there are probably more than one hundred square miles of watered Bermuda grass lawns in the Salt River Valley or Phoenix area. Bermuda grass matures and pollinates in two or three weeks' time, with new blossoms continually, in contrast to most grasses.

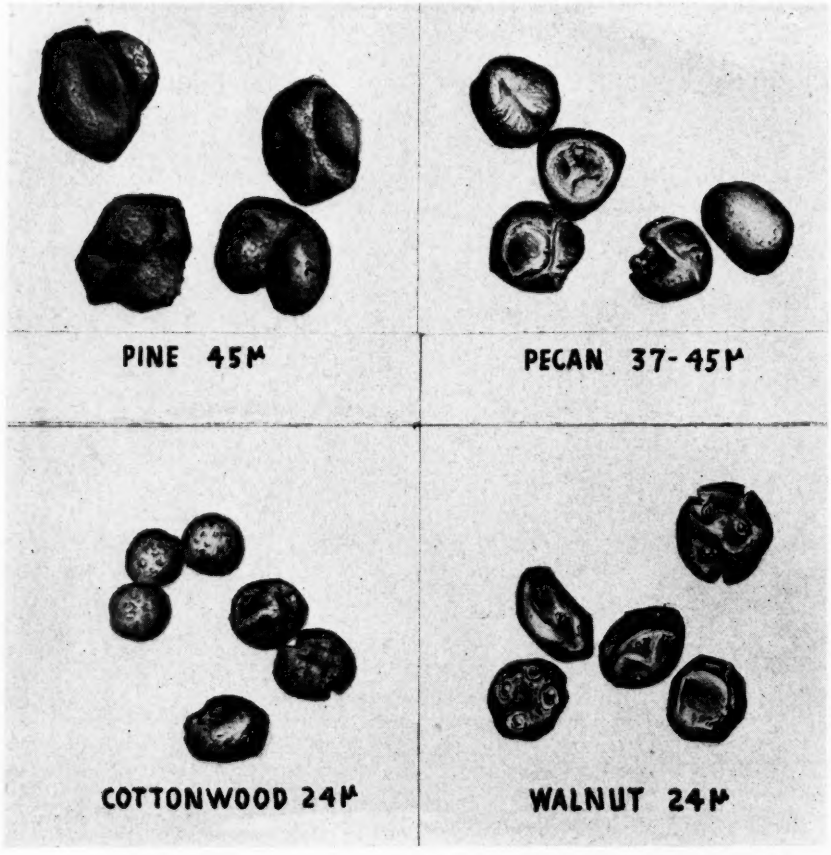

Fig. 3.

Determination of the pollen content of the air by means of counts of exposed slides is an important adjunct to the study of hay fever in any region. In this study we have charted the daily and seasonal variation in pollen concentration in the atmosphere in and around Phoenix from 1934 to 1936, and since that time, sampling of the atmosphere has been carried out at intervals to check on previous counts and therapeutic indications from season to season. The slides in 1934 were exposed on the desert 10 miles north of the center of Phoenix in a small nonirrigated community one mile from the edge of cultivated land. During 1935 and 1936, slides from the nearby desert and the center of town were compared, and in 1936, counts of the pollen in

town were made. During 1935 and 1936, the slides were exposed on a porch near the center of town, and since then, on a window of a tenth floor medical office buildng.

The slides are mounted at a 45 degree angle on weather vane arrangement, protectng them from rain but allowing full exposure to the air. Because the slide automatically faces into the air currents, there is greater volume of pollen deposited on windy days than would be with the slide lying flat on the window ledge. A very thin coating of mineral oil was used, and at the present time glycerin is used.

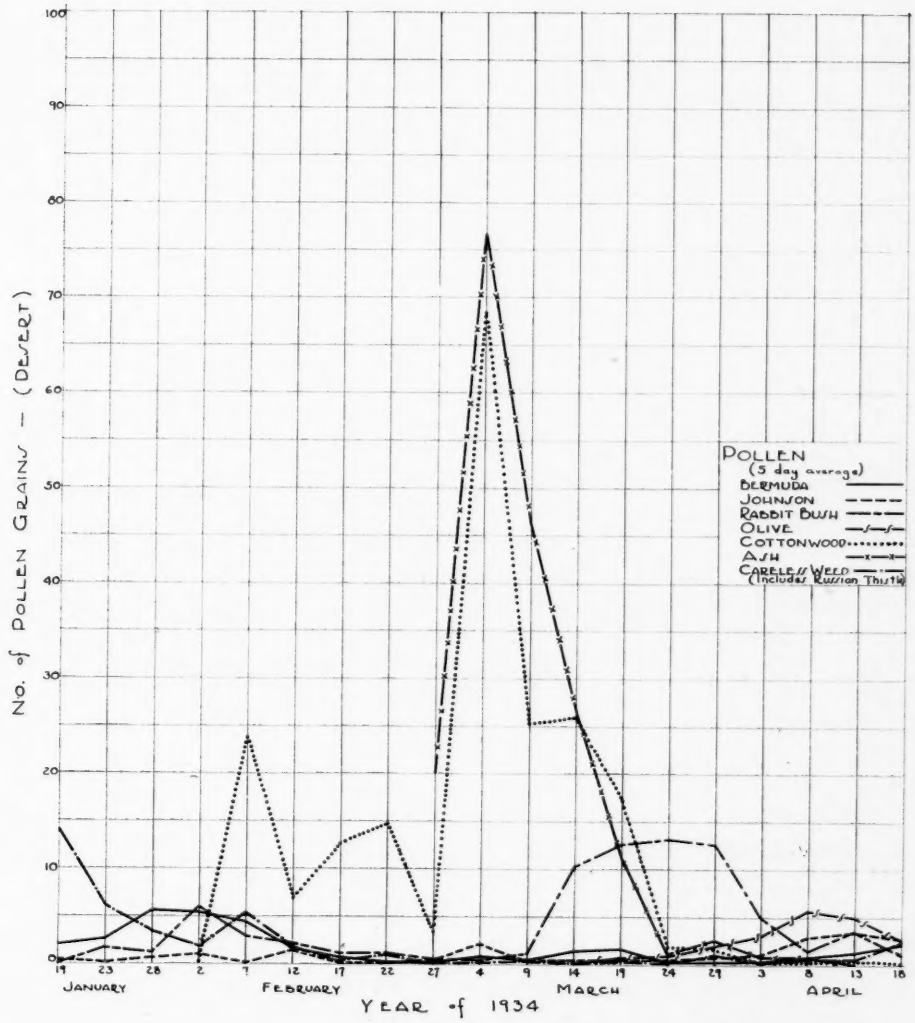

Fig. 4.

The best means of identification is to make comparative sample slides directly from the local pollinating flora by shaking the pollen directly onto the smeared slide or by substituting previously collected and pre-

pared dried pollen. No preservative medium or cover slip is necessary as these samples will keep quite satisfactorily, much better in fact than when mounted in balsam under a cover slip.

The differentiating features are apparently best preserved on the dry slides, as fluid preparations have a tendency to obliterate the surface markings and fill out the pollen grains to a smooth round sameness.

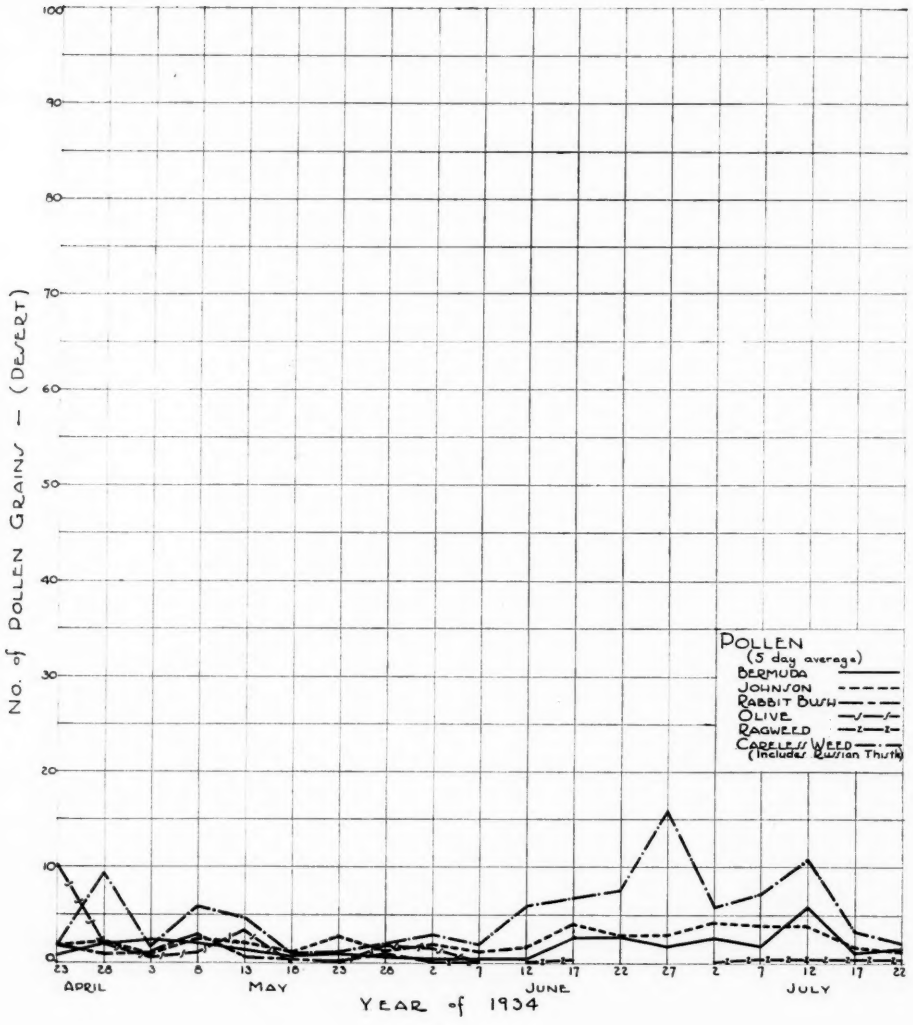

Fig. 5.

If moisture is present, slides may be very gently warmed before counting. The usual area to be covered is 1.8 square centimeters, which has been estimated by Durham[4] to be the pollen content in one cubic yard of air. Ten square centimeters of slide were counted in this study.

Since there may be as much as a 300 per cent variation in sections of the slide, each cross sweep should be taken from spaced areas of ten or fifteen sweeps and the average for five determined.

With study and experience, identification of genera is usually not difficult. There are six families together with a group of miscellaneous trees which are the most frequent causes of hay fever. The families are as follows: (1) Gramineae (grass family, including Bermuda grass, and Johnson grass); (2) Compositae (composite family, including wormwood, ragweeds, rabbit bush); (3) Amaranthaceae (amaranths, including

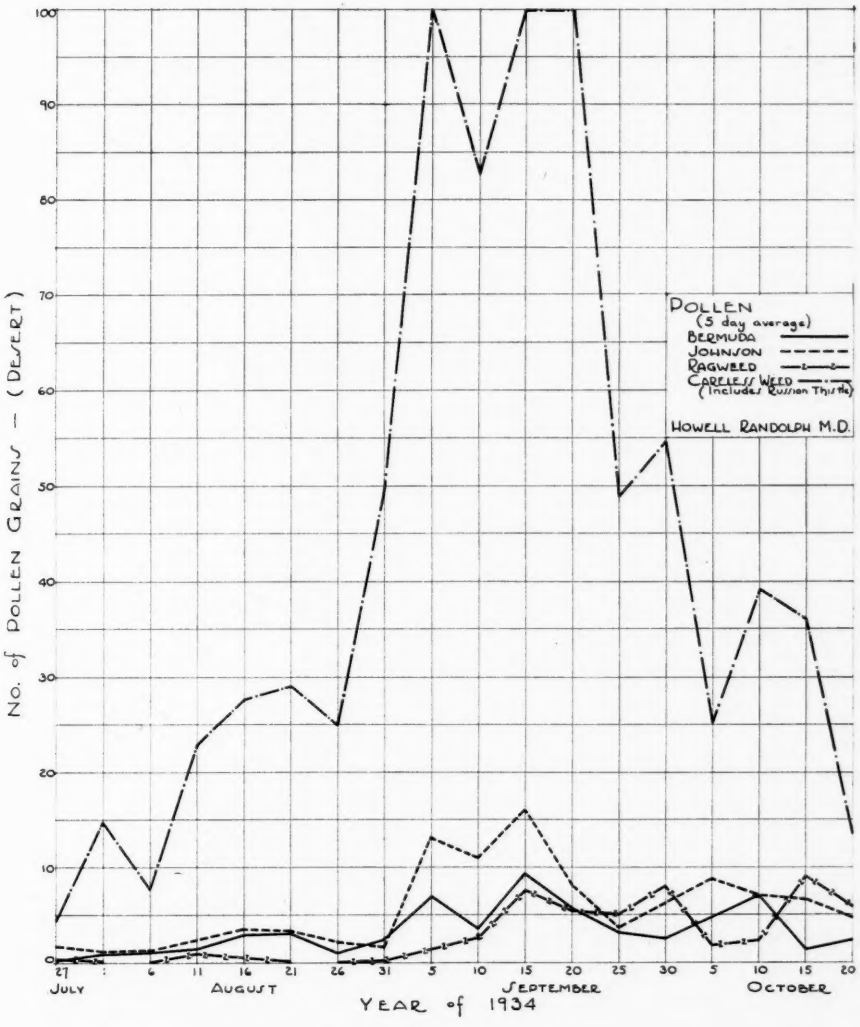

Fig. 6.

careless weed, pigweed, tumbleweed); (4) Chenopodiaceae (chenopods or goosefoot family, including lamb's-quarters, salt bush, Russian thistle, shad scale); (5) Polygonaceae (buckwheat family, smartweed); (6) Plantaginaceae (plantain family).

For routine counts, no attempt need be made to identify species, as the results are disappointing. Genus identification is ordinarily sufficient for clinical application, as the species are closely allied. When

seasons overlap, no reliance can be placed on pollen counts of the morphologically similar species. Atypical forms comprise a small percentage of unidentified pollens, and there may be some error in identification of simultaneously pollinating trees. There is wide variation in size and shape of some pollens, for example, Johnson grass;

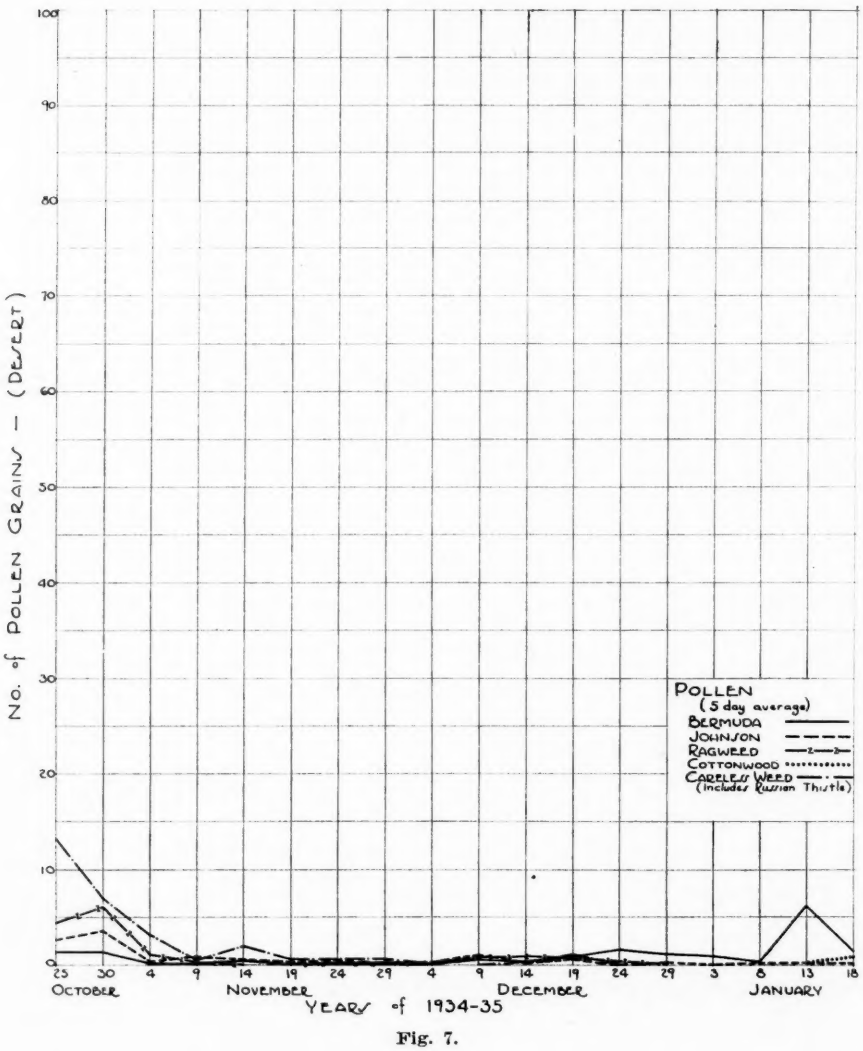

Fig. 7.

much less variation in others, as in careless weed. Grass pollens are occasionally difficult to distinguish accurately, but are clear cells of pale color.

Chenopods and amaranth pollens are very similar to each other. This large group of plants including careless weed, salt bush, Russian thistle, and lamb's-quarters are morphologically practically impossible to differentiate, and the overlapping season renders it necessary to

correlate counts of these pollens with plant incidence, field observation, and patients' behavior. The salt bush and lamb's-quarters are late June and July pollinators, and yet it is our opinion that rarely do these two reach sufficient volume to be clinically significant. We use very little of these two pollens in treatment, although we include them in our routine skin tests.

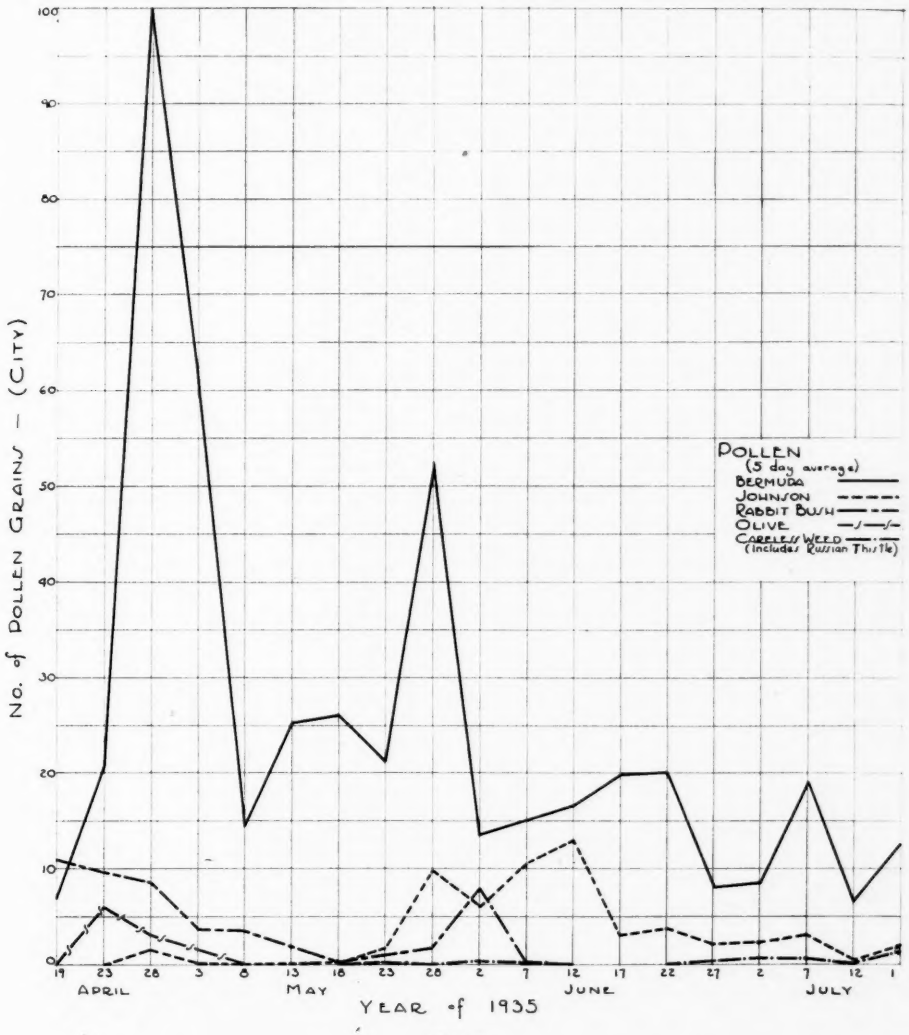

Fig. 8.

The pollen season begins about the first of February with the release of cottonwood (*Populus macdougalii*), followed in about two weeks by ash (*Fraxinus velutina*). The cottonwood pollen ceases in from three to five weeks and is of clinical importance for probably no more than two weeks. The ash season lasts longer and may extend for six weeks from the middle or last of February to the first of April

or after. These are the chief offenders among the trees, but in April and May the olive tree throws off considerable pollen in certain areas of the Valley and may surpass the other tree pollens in importance to those adjacent to olive tree groups. The mesquite tree is common, but its pollen was not shown on the graphs in this study because of its relative unimportance. The season lasts 6 weeks. An occasional pine or walnut grain was found.

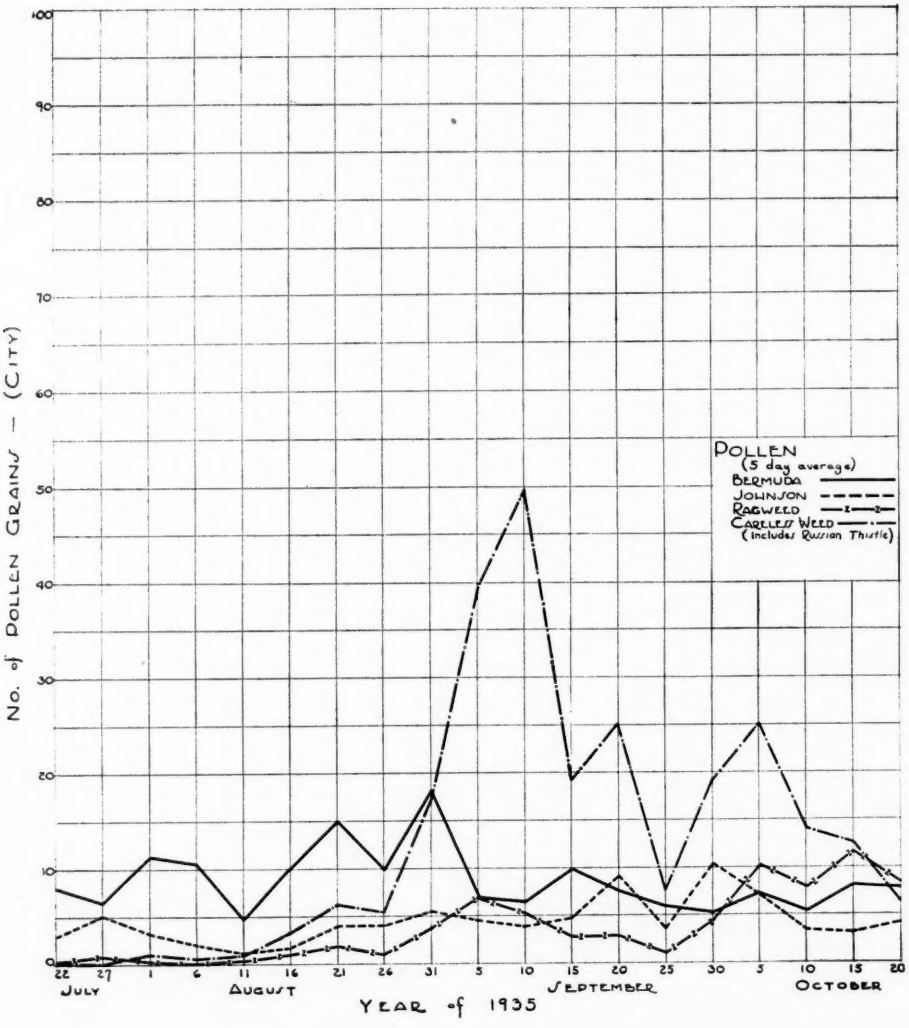

Fig. 9.

In April, depending upon the warmth of the weather, Bermuda grass (*Capriola dactylon*) increases. This is probably the most important offender in this region, because of the length of the season and the persistence of exposure. This pollen continues throughout the summer, diminishing sharply in hot weather, with a second rise in Septem-

ber or late in August. April and May are the worst months for Bermuda grass-sensitive patients. Johnson grass (*Sorghum halepensis*) follows Bermuda grass to some extent and may reach a higher peak in midsummer, but is of secondary importance from the clinical standpoint, as it is a large pollen with low buoyancy. Alfalfa was not differentiated on the pollen slides, but is found to cause some hay fever and asthma among ranch workers. However, the dry hairs and leaf dust are chiefly responsible.

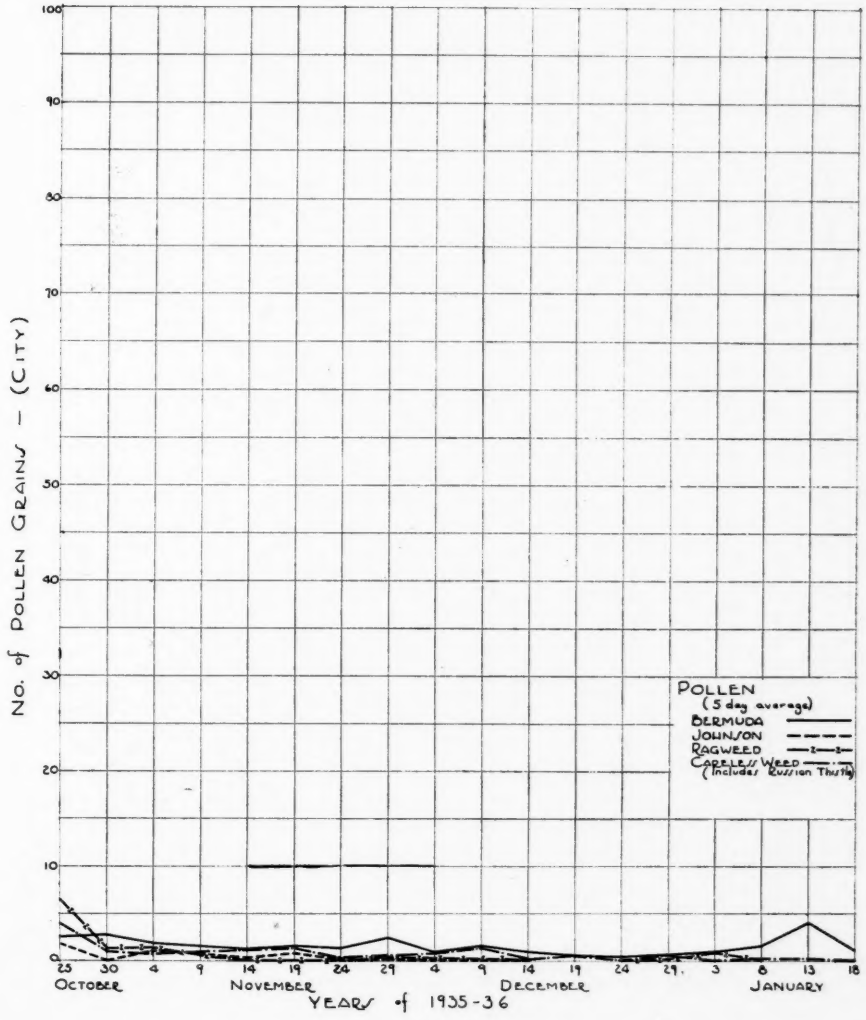

Fig. 10.

An important spring pollinator is rabbit bush (*Franseria deltoidea*). The pollen is similar to that of ragweed, easily identified, and it appears in late March and reaches its peak in April and May. While more troublesome to those on the desert, it is a factor to be reckoned with by

Valley residents, as there is a great deal of pollen if there is more than usual rainfall, and under normal conditions there is sufficient to cause symptoms. It is the smallest and lightest of all our weed pollens.

In 1937 cultivation of sugar beets for seed purposes was begun, and each year between 4 and 6 thousand acres are planted. The seed is planted in the fall; it grows through winter and spring; then it blossoms in April and May. The plant grows to a height of 5 or 6 feet, and

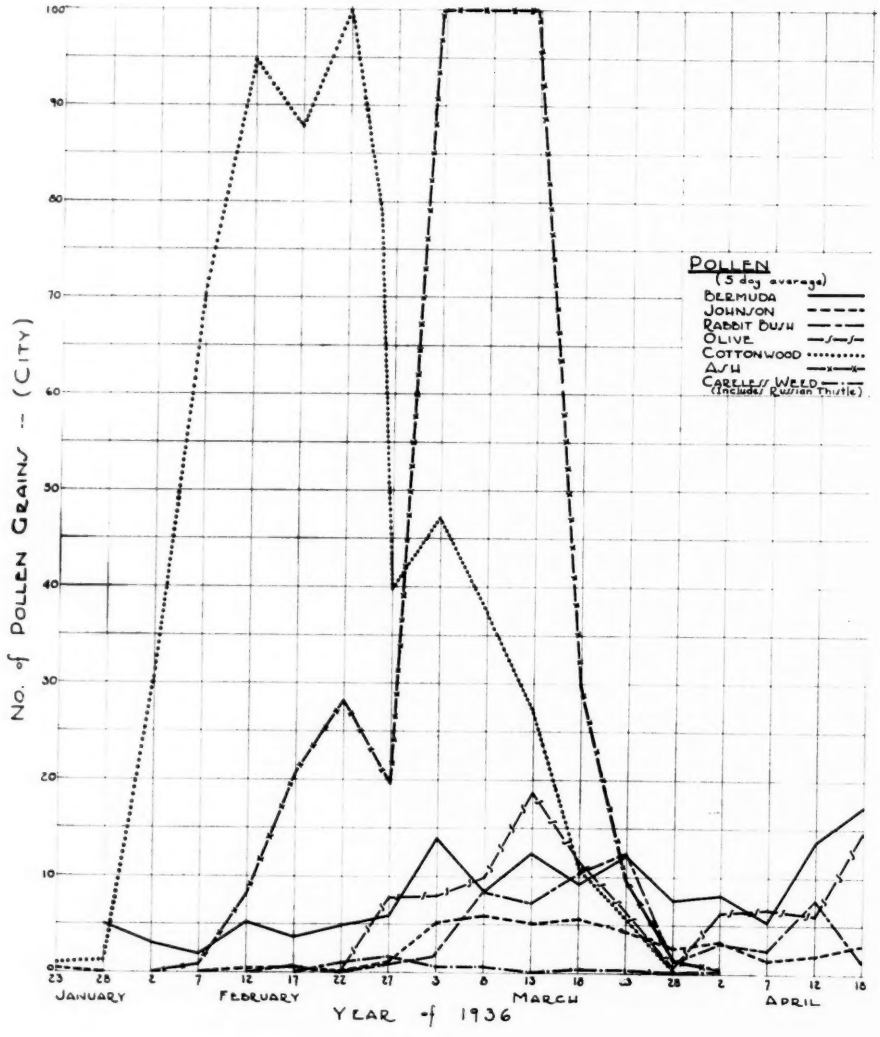

Fig. 11.

produces a rank growth and quantities of pollen. Those living near these plantings suffer most, but it is a factor to be reckoned with throughout the Valley. The seed is harvested in June and July.

Although appearing in small numbers throughout the entire season, careless weed (*Amaranthus palmeri*) is essentially a late summer and

fall weed and is the most important pollen producer from August to November. Russian thistle (*Salsola pestifer*) and slender false ragweed are of less importance. From observation of the Russian thistle plant it seems to have been spreading during the past ten years. The slender false ragweed is not numerous but has to be considered a cause of symptoms in October. The common ragweed, so important in the Midwest, is not found here.

TABLE I

COMPARATIVE TABLE OF POLLEN GRAINS

	DESERT		CITY	
POLLEN	NUMBER	PER CENT	NUMBER	PER CENT
Bermuda	807	8.86	3996	24.28
Johnson	772	8.47	961	5.84
Cottonwood	1055	11.58	2588	15.72
Ash	820	9.00	2674	16.25
Careless Weed	3447	37.83	1575	9.57
Sl. False Ragweed	336	3.69	320	1.94
Rabbit Bush	445	4.88	464	2.82
Olive	206	2.26	405	2.46
Pine	113	1.24	121	0.73
Walnut	25	0.27	24	0.14
Miscellaneous	244	2.67	2038	12.38
Unidentified	841	9.23	1293	7.85
Total Number	9111	99.98	16459	99.98

Table I represents a comparison between the pollen incidence in the city and that one mile from the edge of irrigation. Particularly interesting is the low incidence of spring pollinating pollen on the desert as compared to the city, and the relatively lower total pollen count. A notable exception, however, is the rabbit bush and the fall pollinating careless weed. Probable explanation of the high careless weed count on the desert is the fact that a large part of this pollen is produced in the citrus groves during the fall season when weeds are allowed to grow as a cover crop. These groves are located along the edge of the Valley in a belt about two miles wide, adjacent to the desert.

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THE POLLEN CONTENT OF THE AIR IN RIO DE JANEIRO, BRAZIL

J. B. Greco, M.D., and A. Oliveira Lima, M.D., Belo-Horizonte, Brazil

CONTINUING the study we began about the problem of pollinosis in Brazil, we report, in the present paper, the results of the pollen counts in the air of Rio de Janeiro from May, 1941, to July, 1942. As far as we know, such an investigation is the first of its nature carried out in the capital of Brazil. Previously we reported[1] the result of the pollen content in the air of Belo-Horizonte.

METHOD

The method employed was that commonly used for such studies but with certain modifications. As we live in Belo-Horizonte, about 175 miles north of Rio de Janeiro, we were obliged to devise a method by which the slides could be sent to Rio de Janeiro to be exposed by others especially instructed for that purpose, returning the slides after exposure to enable us to make the necessary counts. Care was taken that all slides were uniformly exposed at a height of about eight meters and at the same time of the day (8 A.M.). We have special boxes constructed to hold 31 slides coated with glycerin jelly and methyl green. The slides were arranged in such a way that they did not touch each other, the boxes having slots both in the box and the lid, thus preventing contact. Two days before the first of each month we sent the boxes to five persons who lived in different districts of Rio de Janeiro. They changed the slides daily, special care being exercised so that the other slides in the boxes were not contaminated. Each day the date of exposure was recorded on the frosted part of each slide. We employed the frosted slides with a free square on the center,[2] as we found them very useful for such a purpose. When all slides had been exposed, the boxes were returned to us to perform the counting of pollen grains and fungi spores. By the time they had already received a new box. The persons in charge were personally instructed by us how to make the necessary exposures.

Five slides in the various districts of the city were exposed daily, one each in Leblon, Ipanema, Botafogo, Laranjeiras, and one in the center of the city itself. As soon as we received the exposed slides, we proceeded to identify the the various types of pollens and fungi, and the counting of same. As the difference in pollen content among the various districts was so small, we decided to make a daily average of the five districts combined.

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RESULTS

The results of our pollen counts in Rio de Janeiro will help considerably in the study of pollinosis in Brazil. As shown in the self-explanatory graphs (Figs. 1 and 2), there is only one pollen season in Rio de Janeiro. This season may be considered from the middle of May to the middle of June. Further, our studies have shown only one type of pollen to be existent, namely, grass pollen. There is also a minute proportion of amaranth-chenopod, but this pollen occurs only infrequently and has no definite season character.

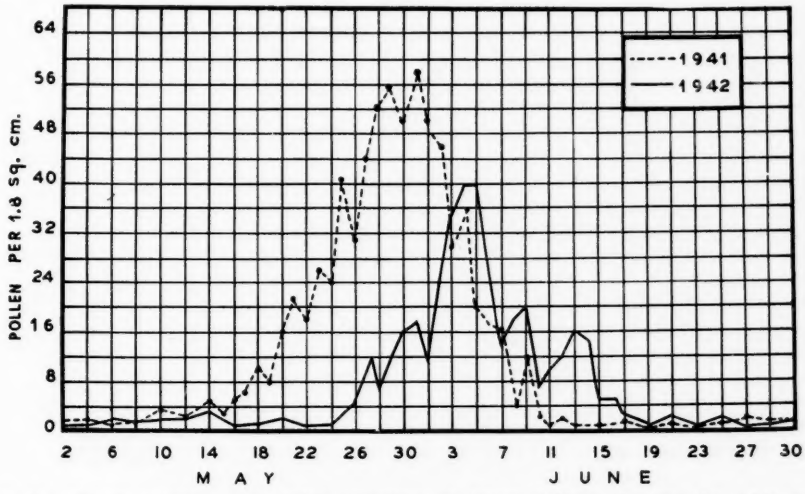

Fig. 1.—Graph showing the daily counting of grass pollens during the 1941 and 1942 seasons.

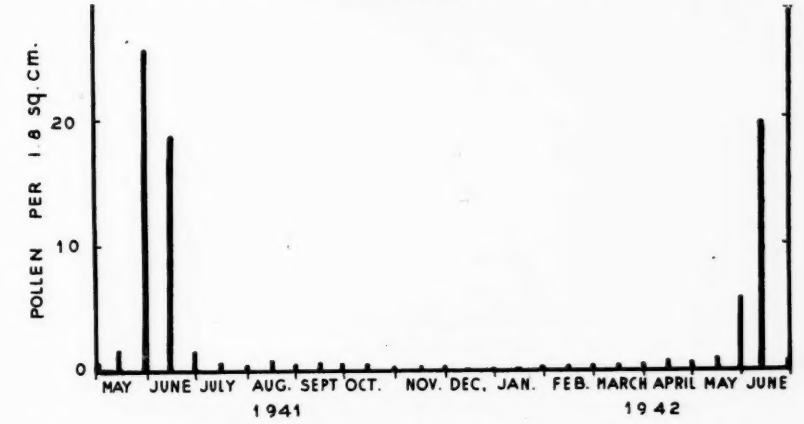

Fig. 2.—Graph showing the monthly fluctuations of pollen counting from May, 1941, to June, 1942.

The pollen season of Rio de Janeiro may be considered similar to that found in Belo-Horizonte[1-4] and other cities in the states of Minas Gerais[5-8] and São Paulo.[9] Mention must be made of the fact that the pollen count in Rio de Janeiro is considerably lower than that encoun-

tered in Belo-Horizonte. The 1942 season occurred about a fortnight later than in 1941, both in Rio de Janeiro and Belo-Horizonte.

As yet we have not been able to ascertain the kinds of grass responsible for the pollen in Rio, because of our being about 600 km. from this city by rail. In view of the widespread distribution and the manner of pollinization during the pollen season, we think it safe to consider *Melinis minutiflora* as the chief origin. It must be noted, however, that in the neighborhood of Rio there exist other kinds of grass, such as *Hyparrhenia rufa, Panicum maximum, Cynodon dactylon*, etc., but we find that *Melinis minutiflora* is the chief source. As already mentioned, the 1942 season started about a fortnight later than in the previous year. This was probably due to the fact that this grass flowered later than in 1941. However, this statement cannot be considered as definite because of the impossibility of differentiation between the various grass pollen by means of the microscope.

Of the five slides exposed, only that of Leblon showed any traces of amaranth-chenopod, and even so the content was so insignificant that it was not worth while taking into consideration. There were also other pollens not mentioned, of unknown origin, but here, too, the content was negligible.

SUMMARY

1. The authors made daily pollen counts of the air of Rio de Janeiro, from May, 1941, to July, 1942.

2. They found only one defined season due to grasses, occurring from the middle of May to the middle of June.

3. They describe the method employed, and append two graphs which are entirely self-explanatory.

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THE ADMINISTRATION OF NICOTINIC ACID AND CALCIUM LACTATE IN URTICARIA

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NICOTINIC acid has been of great value in the treatment of certain nutritional disorders.* It was considered possible that this vasodilator might benefit patients suffering from urticaria and related food allergies.

In several selected cases of giant hives, nicotinic acid was tried in 20 mg. doses given once, twice, and three times daily. Gradual improvement was noted, with reduction of the swelling and itching and complete clearing of the skin in periods of from one to three weeks. Increasing the dosage did not hasten the recovery (See Cases 1 and 2).

When calcium lactate was given in conjunction with the nicotinic acid, the results were remarkable. Nicotinic acid, one 20 mg. tablet given twice daily with meals, and calcium lactate, 5 grains given three times daily with meals, produced marked improvement in twenty-four to forty-eight hours with complete clearing of the skin in three to four days. After the attack subsided, we found that the nicotinic acid could be reduced to one 20 mg. tablet daily for about ten days and then given every other day with discontinuance after one month. The nicotinic acid was given with meals to avoid the flushing and tingling of the skin that sometimes follows if it is taken in the postdigestive state.

Several of the patient have remained free of urticaria and angioneurotic edema for a year and longer. Upon recurrence of the attacks, nicotinic acid and calcium lactate again controlled the exacerbations within three days after resumption of treatment (Cases 3 and 4).

It will be noted in the case histories of J. C. and L. S. that the asthmatic condition present at the time this treatment was given likewise improved. However, in administering this therapeutic routine to a group of patients with chronic asthma, now being studied, we have observed improvement only in those thin, emaciated individuals in whom malnutrition of undetermined cause was evident.

We have used this nicotinic acid and calcium therapy in fifteen cases of urticaria with gratifying results. Although there are too few cases from which to draw any general conclusions, we report the evidence to stimulate repetition by those who may have the opportunity to study like cases.

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*Youmans, John B.: Nutritional Deficiencies, J. B. Lippincott Co., 1941.

CASE REPORTS

Case 1.—C. G., white female, aged 56 years, complained of "giant hives" of two years' duration. Diets, laxative salts, and calcium had been tried without improvement. All scratch tests negative. After nicotinic acid, 40 mg. daily by mouth, a gradual improvement occurred, with hives practically clear after fourteen days. Hives returned on the twentieth day when the patient's medicine had been exhausted two days before. Treatment was resumed for two months with occasional slight attack of hives. After treatment was stopped, hives returned in three days. Treatment was again resumed, and the skin cleared immediately. Subsequently, this patient was able to control the urticaria by taking 20 mg. of nicotinic acid every other day.

Case 2.—E. K., white female, aged 52, complained of "hives" of five months' duration. She had had asthma at 10 years of age with occasional attacks since. Scratch tests showed feathers positive. She was given 40 mg. of nicotinic acid orally per day. Two weeks later the urticaria was much improved. Treatment was continued for two months, when the patient reported no further skin irritation and failed to return.

Case 3.—L. S., a colored female, aged 26, complained of "asthma and hives." Scratch tests were positive to cat hair, dog hair, feathers, and house dust. Asthma improved upon elimination of epidermals in the environment. Nicotinic acid was given orally, 40 mg. daily for three weeks with slight improvement of urticaria. The calcium lactate in 5-grain doses was added three times daily. She was free from hives in two days. Treatment was discontinued after one month. Two years later this patient returned with severe urticaria which cleared within three days of resumption of treatment. Five months later this patient returned with severe asthma and hives which the patient attributed to exposure to fresh paint. Treatment was resumed with prompt disappearance of hives and asthma.

Case 4.—J. C., a white male, aged 11, suffered large swellings on the head and face. He could not get his hat on over the swellings, one eye partly closed by swelling on the forehead. His mother stated that he frequently had "hives and red rash" all over his body. He had been admitted to the emergency room for treatment and complained of pain in his chest and difficult breathing. He received nicotinic acid, 20 mg., and calcium lactate, 15 grains, daily. Angioneurotic edema was entirely clear in three days, the chest was clear, and the patient was normal in appearance. Two years later he returned with angioneurotic edema. Treatment was resumed with recovery in three days. He was observed one year later when he stated that occasional recurrences were controlled by resumption of treatment for one week.

Case 5.—A. P., a white male, aged 11, complained of hives of one week's duration. He received nicotinic acid, 20 mg., and calcium lac-

tate, 15 grains, per day. The skin cleared in four days. There was no recurrence when observed two months later. Scratch tests were negative.

Case 6.—M. T., a white female, aged 48, complained of hay fever and urticaria. She was sensitive to grass and ragweed pollens. During June and July, when hay fever was most severe, the exposed surfaces of the body "broke out in red splotches which itched intensely." Nicotinic acid and calcium lactate in usual dosage controlled the urticaria, but had no apparent influence on the hay fever.

SUMMARY

1. Nicotinic acid with calcium lactate was found to be effective in a small series of patients with urticaria.

We acknowledge with thanks the generous supply of nicotinic acid tablets furnished us for these clinical studies by the Mead-Johnson & Co., Evansville, Ind.

HISTAMINIC CEPHALGIA

Report of a Case

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A NEW syndrome of vascular headache specifically responsive to histamine desensitization has been recently described by Horton.[1] Histaminic cephalgia, as it was named by that author, is characterized by attacks of severe unilateral headache and lacrimation without nausea and vomiting. The attacks are usually frequent, to a large degree incapacitating, and can be induced by the subcutaneous injection of histamine phosphate or diphosphate. Such induced attacks are identical with the spontaneous attacks. Temporary relief is obtained by the administration of epinephrine, and the attacks can be eradicated for varying periods by desensitization to histamine. Relapses may be again controlled in the same manner or prevented by a maintenance dose of histamine.

As yet, few reports of this syndrome have appeared. The very excellent results of treatment should be re-emphasized, since serious disability may be so readily eliminated.

CASE REPORT

A 37-year-old housewife came to the University Hospital, May 21, 1941. She stated that she had been troubled with occasional headaches nearly all her life, but that for about four years she had been having frequent extremely severe headaches unlike any previous difficulty. These severe headaches were always alike except for variable duration. They were unilateral, involving the left side of the head from the left frontal area to the occiput. As the headache progressed during an attack, injection of the conjunctival vessels and puffiness of the eyelids of the left eye would appear, and occasionally the swelling of the lids would literally close the eye. The duration of the headaches varied from several hours to all her waking hours. Often sleep came only as a result of exhaustion. Daily attacks had occurred for as long as four weeks. During free intervals she felt perfectly well and was active normally in every respect. In four years no free interval had lasted longer than five or six weeks.

All ordinary analgesics ranging from aspirin to morphine had failed to relieve the pain. If the pain occurred, daily nausea and vomiting

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developed, and in prolonged episodes it had been necessary to supply fluids parenterally.

Physical examination on May 21, 1941, at which time she was symptom-free, was completely negative except for slight constriction of the left visual field for which no explanation could be found. On May 22, 1941, a spontaneous headache developed with left conjunctival injection, as shown in Fig. 1. Routine allergy skin tests were essentially negative. One-tenth mg. of histamine phosphate injected intradermally produced a large cutaneous wheal and induced a typical headache. Five minims of adrenalin given subcutaneously relieved the headache in thirty minutes.

A diagnosis of histaminic cephalgia was made and desensitization to histamine attempted. One-hundredth mg. injected subcutaneously as the first dose again reproduced the headache. Following cessation of the headache, 0.005 mg. was given, but with the same result.

Fig. 1.—Unilateral conjunctival injection during an attack.

On the following day, a spontaneous attack appeared and lasted throughout the day. Similar spontaneous symptoms recurred daily for five days, and after the second day, severe nausea and vomiting developed so that normal saline and glucose solutions were given intravenously to maintain adequate fluid intake. During this period barbiturates and codeine had virtually no effect on the pain. No further histamine was administered for fear of increasing the already severe distress. Instead, oral administration of histaminase was resorted to as an alternative and more conservative measure. Fifteen units were given three times daily. Within three days all symptoms disappeared. Three days later she was discharged from the hospital feeling well. No recurrence has occurred up to August 1, 1941.

COMMENT

It is difficult to explain the apparent discrepancy between the large number of patients diagnosed as having histaminic cephalgia by Horton and his co-workers in less than three years and the fact that this patient is the first one with this syndrome recognized at the University Hospital. It is possible that such cases have escaped detection. In addition, the variation in incidence may be partially ascribed to the fact that University Hospital patients are nearly all from Iowa, while those seen by Horton come from a wide range.

Horton specifically stated that nausea, vomiting, and visual disturbances do not accompany the attacks of pain in histaminic cephalgia. The presence of these symptoms in my patient makes it appear that Horton was too conservative in his delineation of the manifestations of the syndrome. This case certainly fulfilled all of the other diagnostic criteria and, in addition, the patient responded to treatment.

Extreme difficulty in desensitization to histamine, which has not been previously recorded, was encountered in this patient. The administration of histaminase was accordingly the alternative. This suggests that in some instances histaminase is preferable to histamine in treatment, because any possibility of increasing the symptoms even temporarily is eliminated, although no harm has resulted from such use of histamine.

SUMMARY

1. The first case of histaminic cephalgia recognized at the University Hospitals is reported. This is in contrast to the large number of cases reported by Horton.

2. It is suggested that nausea and vomiting associated with unilateral headaches do not alter the diagnosis in favor of migraine, provided the symptom complex is otherwise similar to that described by Horton and can be reproduced by histamine.

3. Difficulty in desensitization to histamine is recorded.

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ALLERGY TO ODOR OF WHITE POTATO (IRISH POTATO)

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ATTENTION has been called[1] to the importance of the factor of food odors or vapors in the etiology of infantile eczema. The report presented here is that of an asthmatic child whose sensitivities included, among other things, the white potato. Control of this patient's symptoms occurred only after complete removal of potato from the environment.

CASE REPORT

Asthma developed in this boy (N. H.) at the age of 2 years. He had previously had infantile eczema. The symptoms occurred the year around but appeared to be worse in spring and fall. The family history for allergy was negative.

Physical examination at 4½ years of age was negative except for a mild emphysema. Skin tests by the scratch method showed the following positive reactions:

Barley	+	Cat dander	++
Corn	++++	Dog dander	+
Carrot	++	Feathers	+
Turnip	+++	House dust	+
White potato	++++	Sheep dander	++
		Ragweed	++

Removal of foods from his diet and hyposensitization to dust and pollen produced definite improvement but not complete control of the symptoms. After eighteen months of treatment he suddenly became worse. Attacks occurred two or three times weekly. This state of affairs persisted for five months with only two periods of complete relief—once during a seven-day period when he was hospitalized and once during a ten-day period when the patient was confined to his bedroom on strict dietary precautions. When the patient was allowed free use of his home, the attacks occurred as usual.

A visit to the home just after a severe attack and a detailed history of all events immediately preceding the attack revealed that this patient was feeling very well until he came into the kitchen. No cooking was being done but the maid was peeling potatoes. The child began to cough violently and soon developed a severe attack of asthma. It was recommended that potatoes be removed entirely from the home. This procedure dramatically stopped his attacks. He remained entirely free from them for three months. At this time the parents attempted to

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bring some canned potatoes into the house, and a severe attack of asthma in the boy immediately ensued. These potatoes were on the stove cooking when the attack occurred. This attack was different from the previous ones in that this was provoked by the commercially canned white potato. The parents had never used canned potatoes before. They purposely used them this time in the hope that the previous attacks were caused by the peelings or dust from the peelings. The commercially canned potatoes are put up in salted potato water after being carefully peeled and cooked. This attack proved that the patient's sensitivity was not due to the potato peeling or to any insecticide or fertilizer contained on it.

Follow-up examination two years later revealed that this patient has had only one attack of asthma in that period. This occurred when another attempt was made to bring potatoes into the home. For the past twelve months no further attempts have been made. The parents continue to do without potatoes and the child has remained free of asthma.

To sum up, this patient developed severe asthmatic attacks by the ingestion of cooked white potato, and by the presence of potato in his environment whether raw or cooking. The potato peeling was not a necessary factor in the provocation of his attacks.

COMMENT

Allergic symptoms from food odors have been described previously,[1, 2, 3] but the literature on this subject is extremely meager. All of these reports have emphasized the influence of vapors or odors emanating from foods during the process of cooking or frying. Feinberg and Aries[2] in 1932 reported three cases of asthma from food odors—from the cooking of shrimp, peas, beans, and lentils. Coca[3] mentions specifically that the frying of fish may induce asthma in markedly sensitive children.

In the case reported here, cooking was not essential to the production of symptoms. Asthma was precipitated by the mere presence of the food in the child's immediate environment. Symptoms were not controlled until the food was entirely removed from the house.

Sensitivity to food odors is very easily overlooked by the most competent of allergists. Unless this possibility is kept in mind, many patients will continue to have symptoms from foods which they never ingest. Parents do not think of this possibility and the child never complains that certain odors bother him. This type of sensitivity occurs frequently in patients with infantile eczema. It is probable that its occurrence is not infrequent in patients suffering from asthma and other allergic conditions but that it is merely overlooked. It is hoped that this route for the production of allergic symptoms will be kept in mind especially in the treatment of those patients who have failed to respond to the usual procedures of food elimination and hyposensitization.

SUMMARY

1. A case of asthma in a young child is reported. The condition was due to the presence of potatoes in the environment.

2. Complete relief was obtained by removal of the potatoes from the home.

3. It is suggested that this route for the production of allergic symptoms be kept in mind by physicians and parents.

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VITAMIN B_1 HYPERSENSITIVITY WITH DESENSITIZATION

Report of a Case

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THE extensive use that is made of vitamins, and especially of vitamin B_1 or thiamine hydrochloride, makes this modest article of interest since it shows for the first time in the medical literature, according to our careful review, the possibility of hypersensitiveness to this product. Because of the extensive use of vitamin B_1 in many countries, it is hard to believe that no other cases of allergy to thiamine have existed. However, in specialized books of this affection consulted by us, and in many medical magazines within our reach, we have never seen it mentioned.

CASE REPORT

A. E. Y. S.—15-year-old female student, single, born in Cuba, and of the white race.

Family History.—Parents and one brother are alive and healthy; two brothers are dead of unknown cause. In the family we found no allergic antecedents. Her mother suffers from occasional headaches.

Past History.—At an early age the patient suffered from whooping cough. Tonsil operation was performed last year. She has had a mild attack of rhinitis and asthma.

Present Illness.—The patient consulted Dr. Lino Mederos, because she presented rheumatic pains in both legs, not associated with arthritis. When she was 2 years old she suffered from asthma and was three years under the care of Professor Valledor. Now she has only wheezing with colds. There are no other respiratory, digestive, circulatory, urinary, nervous, or general symptoms.

Dr. Mederos indicated as the only treatment injections of 50 mg. of thiamine hydrochloride daily of a Cuban trade mark of repute. On the day following the first injection, she had a maculo-pruriginous eruption on the face, chest, and on the back (where it was of great intensity and extent). Sometime later she was given 3 similar daily injections and the eruption appeared again with the same characteristics. Dr. Mederos then prescribed intramuscular injection of sodium-magnesium hyposulfite. The eruption disappeared, but when she was injected with thiamine, the eruption appeared again. Once she was injected on the same day with thiamine and hyposulfite, and the eruption disappeared. Dr. Mederos then turned the case over to me for an allergic study.

Presented at the Staff Meeting of the Havana City Hospital, "Freyre de Andrade," June 1, 1943.

Physical examination was normal. Laboratory tests, including blood count, Kahn test, blood sugar and urea, urinalysis, stool examination, and roentgenogram of the chest were all within normal limits, with the exception of a 5 per cent blood eosinophilia.

With this information, and through the kindness of the director of the laboratory producing the thiamine and in the presence of his representative, we proceeded to make the test (given in Table I) in the anterior region of both arms, injecting intradermally 0.02 c.c. of each product.

TABLE I

MATERIALS	DEGREE OF REACTION
Histamine	++
Product of the laboratory	+++
Product of Winthrop	+++
Product of Funk Dubin	+++
Product of Lab. Linner	+++
Product of Squibb	+++
Separating the ingredients of the commercial product:	
Hydrochloride of thiamine	+++
Clorobutanol	negative
Saline solution	negative

TABLE II

MATERIAL	DEGREE OF REACTION	CONTROL
Histamine	++	++
Studied Product	+++	negative
Product of Winthrop	++	negative
Product of Funk Dubin	++	negative
Product of Linner	++	negative
Product of Squibb	++	negative
Hydrochloride of thiamine (pure)	+++	negative
Clorobutanol	negative	negative
Saline solution	negative	negative

There was no general or other reaction.

We then took 10 c.c. of blood from the patient in a sterile tube, centrifuged it, and immediately did passive transfer, injecting 0.05 c.c. in different places on the arm of her mother. After forty-eight hours we injected intradermally at the sensitized sites 0.02 c.c. of the products listed in Table II.

After two days, we studied the leucopenic index, and used 6 tablets of 1 mg. each of thiamine hydrochloride of Glaxo:

Leucocytes fasting ---------- 10,000 per cu. mm.

One hour after taking the 6 tablets---------- 8,000 per cu. mm.

With this information we feel justified in affirming that this patient is allergic to thiamine.

We then prepared the product of the commercial laboratory first used in dilutions with physiologic saline solution as follows: 1:5,000, 1:1,000, 1:100, and 1:10. The patient received daily subcutaneous in-

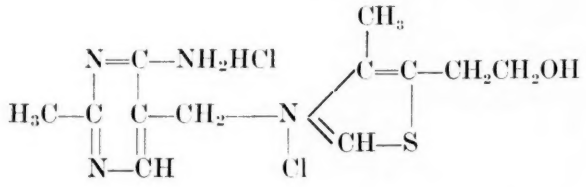
jections starting with 0.1 c.c. of the highest dilution with increasing increments of 0.1 c.c. daily, until she was inoculated with 1 c.c. containing 100 mg. of thiamine. She was then injected for ten consecutive days with 100 mg. with no signs of local or general reaction.

Three months afterwards, the intradermal tests were repeated with 0.02 c.c. of the thiamine hydrochloride, clorobutanol, and saline solution, all of which were negative.

We consider, then, that this case of allergy to thiamine was desensitized.

DISCUSSION

Since 1936, when Jansen and Donath isolated vitamin B the natural product itself, as well as in preparations of B complex, has been in wide use. In 1936 the synthesis of vitamin B_1 revealed the following formula:



We believe that even though the molecule of thiamine does not contain any protein, that is no obstacle to its allergenicity. The existance of semiantigens or haptens has been demonstrated. They result from the union of a protein with a nonprotein element. We know from the experiences of Wolff-Eisner that some drugs combine with proteins of the blood or of the tissues, and the product acts as a foreign protein to the same organism. Also, the ideas of Landsteiner demonstrated that the complex is specific to the organism and is completely independent of the chemical group that generated it. We suggest that the thiamine hydrochloride in the case that we present was transformed to an azoprotein of thiamine, and this was responsible for the reaction of the patient.

A point of interest that we should like to discuss is that the patient presented the eruption after the *first* injection of thiamine, and, according to our questionnaire, a posteriori, she had never been injected with vitamin B_1. Of course, we cannot prove that she used this medicament before, but the principle of the vitamins is that they are found in the food in such a quantity that with a normal diet, a considerable amount is doubtless ingested and absorbed. However, she did not have a previous eruption. This proves that a phenomenon had taken place: that the organism was sensitized biologically with the natural thiamine and responded allergically to the crystallized form.

SUMMARY

1. We herewith present (according to our inquiries) for the first time a case of allergy to vitamin B_1.

2. When the intradermal tests were made with products of five different laboratories, the results were all positive. When tests were made with the ingredients of the commercial product, only thiamine produced intensely positive reactions.

3. On the passive transfer a positive reaction to thiamine was obtained.

4. The patient was injected daily with increasing doses of a solution of thiamine hydrochloride until she tolerated 100 mg. daily for ten consecutive days without untoward reactions.

5. The intradermal tests after desensitization were negative.

My most sincere thanks to Dr. Mederos and his assistant, Martinez Araujo, for their kindness in turning the case over to us, and for their cooperation and interest in the clinical study of it; also to Miss Raquel Mitrani, who kindly translated this article into English.

Society Proceedings

MINUTES OF THE MEETING OF THE ADVISORY BOARD OF AMERICAN ALLERGISTS, DEC. 4, 1943

THE meeting was called to order at the University Club at 8:30 P.M. Those present were: Drs. Alexander, Gay, Piness, Rackemann and Cooke.

Applications for examination for certification in allergy referred by the American Board of Internal Medicine were next considered. Approval was given to the following:

Anglin, Dr. George C.	Toronto, Canada
Brust, Dr. Raymond W.	Philadelphia, Pa.
Hampton, Dr. Stanley F.	St. Louis, Mo.
Messer, Dr. William	Brooklyn, New York
Morton, Dr. Wallace	Ft. Sam Houston, Texas
Shuey, Dr. Charles B.	Dallas, Texas

Following the usual practice, Dr. Anglin was recommended for certification in allergy without examination, as he was so certified in internal medicine. The Board then reviewed recommendations for training in allergy as a prerequisite for examination for certification in allergy by the American Board of Internal Medicine. These recommendations as published in the JOURNAL OF ALLERGY, volume 14, page 91, November, 1942, were considered acceptable without change.

Application for certification of allergy clinics was taken up. No clinic was certified. This Board relied solely upon clinic data and case histories submitted. In all cases the records examined were incomplete and unsatisfactory as to history, general medical examination, allergy study, and treatment. The Board discussed the present method of examination of clinics and is aware that it is not wholly satisfactory. Independent personal surveys of each clinic would be ideal, but facilities for such procedures are not available now.

Consideration was given to the future of this Advisory Board in relation to the newly formed Academy of Allergy, but no action was taken and no definite policy outlined. (While this is still under study, the Executive Committee of the Academy of Allergy reappointed the existing Committee for the ensuing year.)

ROBERT A. COOKE.

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

Allergic Rhinitis and Asthma in Hawaii. Young, C. T., Cook, W. R., and Kawasaki, I. A.: War Med. **3**: 282, 1943.

A series of 222 cases of allergic rhinitis and asthma, comprising mostly service men from the United States mainland, was studied in the allergy clinic of the Tripler General Hospital at Honolulu. In this group there were 114 patients with exogenous asthma, 51 with endogenous asthma, and 57 with allergic rhinitis. The course of both allergic rhinitis and asthma was found to be more severe in Hawaii than on the mainland. The endogenous cases were particularly bad during the rainy season (November to March). The latter group, as compared with the exogenous group, contained a larger proportion of those who had never had allergic symptoms on the mainland. The entire group was tested with the common native and mainland pollen, as well as to local dust, stock dust, and to other common inhalants. Of the pollen, the algeroba (Kiawe tree) is regarded as the most important. Next in importance are the pollens of the local grasses. The ragweed, amaranth, and chenopod plants were not found to constitute a problem in Hawaii. Reactions to dust extracts were even more common than those due to pollen, the extracts obtained from local dust showing greater potency. The authors are of the opinion that the diagnostic and therapeutic efficacy of local dust is due to its content of local pollen, fungus spores, and plant debris. Satisfactory results were obtained in the exogenous cases by desensitization with extracts of local dust, grass pollen, and algeroba pollen. This report does not contain numerical data on plant, pollen, or mold surveys.

The Therapeutic Value of Roentgen Treatment in Chronic Asthma. Hull, W. M., Balyeat, R. M., and Chont, L. K.: Am. J. Roentgenol. **49**: 227, 1943.

The authors report their results of roentgen therapy in a large series of cases of chronic asthma. They employed the "cross fire" technique in which six field areas of the chest are irradiated. Two fields are irradiated at one sitting, each receiving about 100 r. Each field is generally irradiated twice during the course of treatment. The total dose is between 800 and 1600 r. Where there is evidence of sinus infection, irradiation of the latter is also done.

The initial effect of the roentgen therapy was observed to be the coughing up of large amounts of thick mucus. Improvement generally occurred within two or three weeks. Excellent results were obtained in 39 per cent, and good results in 40 per cent. It was noted that radiation therapy was of value in those asthmatic patients who showed infection either of the bronchi or the nasal sinuses. There was little effect of this type of treatment in those who were free from infection.

Cardiovascular Allergy. Davison, H. M., Thoroughman, J. C., and Bowcock, H.: South. M. J. **36**: 560, 1943.

In fifteen cases presented, the authors claim that cardiac symptoms were of allergic origin. These patients had either tachycardia or paroxysmal tachycardia, and in one of these there were attacks alternating between auricular paroxysmal tachycardia, auricular fibrillation, and auricular flutter. The majority showed no evidence of organic cardiac disease. All of the patients had other accepted manifestations of atopy, such as asthma, hay fever, and urticaria. In some the cardiac symptoms could be precipitated experimentally by the ingestion of the suspected food. In others, the patient refused to try such an experiment. In seven of these cases, the cardiac symptoms have been controlled by dietary regulation. In two, the symptoms have not been relieved. The remaining six have either discontinued treatment, are still in question, or have lost contact with the authors.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Acquired Hypersensitivity to the Chlorinated Ethlamine Vesicants. Goldman, L., and McNary, R.: Arch. Dermat. & Syph. **48**: 15, 1943.

In an individual known to be sensitive to mustard agent, the application of a trichlorotriethylamine hydrochloride to the skin caused slight disturbances. Ten days later, the application of the free amine caused a local reaction and a papulovesicular reaction about the healed areas, which had been affected by the hydrochloride. Subsequently there was a severe eczematous reaction on the entire forearm.

The Production of Bullae in the Skin of the Duck. Goldman, L.: Arch. Dermat. & Syph. **48**: 161, 1943.

In the search for an experimental animal the skin of which reacts to various irritants with the production of bullae, the author investigated the chicken, the owl, and the duck. The plucked skin of the duck was found to be the most satisfactory. The intradermal injection of saline solution resulted immediately in the production of a large bullous

area, in portions of which the epidermis was separated from the underlying cutis. The application of 50 per cent croton oil produced erythema and edema, followed by large blisters. The application of 50 per cent mustard oil produced a vesicular reaction in about thirty minutes. An hour after the appearance of these vesicles, new ones appeared in the skin surrounding the area treated.

Immunology

UNDER THE DIRECTION OF M. WALZER, M.D., AND MURRAY ALBERT, M.D., BROOKLYN

Studies on the Specific Mechanism of Serum Sickness. III. Passive Sensitization With Antibody Contained in Serum Sickness Convalescent Serum. Karelitz, S., and Glorig, A.: J. Immunol. **47**: 121, 1943.

The presence of transferable antibodies in the sera of patients convalescing from serum sickness was demonstrated by the Prausnitz-Küstner technique, by the reverse technique, and by the method of localized passive serum sickness described by Voss. The presence of serum sickness antibody was demonstrated by the Voss method on sixty-four children convalescing from contagious diseases. These children received instracutaneous injections of undiluted or diluted horse serum on the forearm. After eighteen to thirty hours, they were injected intravenously with 2 to 10 c.c. of serum sickness convalescent serum (SSCS). Forty-nine of the sixty-four children developed a wheal at the prepared site, usually within thirty minutes after the intravenous injection. In some instances, the reaction occurred after one to three hours. A cutaneous area which had been the site of a positive reaction failed to light up again when a second intravenous injection of SSCS was administered twenty-four hours later. The intracutaneous injection of SSCS into sites previously prepared with horse serum produced a local reaction, but failed to inhibit wheal formation when an intravenous injection of SSCS was given subsequently. Normal horse serum was found to be as effective as therapeutic horse serum for the preparation of the skin site. Highly purified therapeutic horse sera, such as scarlet fever antitoxin and diphtheria antitoxin, were less satisfactory for skin preparation. The specificity of the reaction was demonstrated by preparing skin sites in children with hog, sheep, cat, dog, human, monkey, rabbit, and horse serum. When the SSCS was given intravenously twenty-four hours later, reactions developed only at the sites prepared with horse serum. Heating the SSCS at 56° C. for ninety minutes failed to destroy the serum sickness antibody. The production of passive serum sickness did not appear to depend on the presence of precipitin, since convalescent sera which lacked demonstrable precipitin could induce passive serum

sickness and vice versa. Eight of the ten serum sickness convalescent sera employed in these experiments contained serum sickness antibody. The antibody was also demonstrated in two sera obtained from horse-serum-treated patients who failed to develop serum sickness.

In another series of experiments, sensitizing antibodies in SSCS were demonstrated by the usual Prausnitz-Küstner technique and by the reverse technique. Normal subjects were injected intracutaneously with SSCS, and the sites were tested forty-eight hours later with horse serum, normal human serum, and serum obtained from a child forty-eight hours after treatment with scarlet fever antitoxin. Positive reactions were obtained in the sites tested with horse serum and with the serum of the child treated with horse serum. Passive sensitization of human skin was successful with several batches of SSCS, but failed with one SSCS which had also failed to induce local passive serum sickness by the Voss method. Sensitizing antibody was also demonstrated in SSCS by injecting patient's serum and horse serum in the reverse order. The preparatory injections were made intracutaneously with horse serum and the sites were tested forty-eight hours later with SSCS.

Blood was drawn at intervals of twenty-four, forty-eight, and seventy-two hours after patients had been treated with scarlet fever antitoxin. It was found that the blood sera of these patients were more antigenic than natural horse serum for local passive transfer experiments.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Panel Discussion on Allergy and Immunotherapy. Ratner, B., Longcope, W. T., Cannon, P. R., Alexander, H. L., and Bigler, J. A.: J. Pediat. **23**: 231, 1943.

Ratner pleads for a more critical use of sulfonamides and warns about their possible sensitizing effect. Longcope reviews the recent work on fractionation of serum proteins and the means employed in denaturing them. The mechanism and clinical manifestations of serum sickness are discussed, as well as its pathology, both clinical and experimental.

Cannon reviews the early nonspecific illustrations of the anamnestic reaction with typhoid vaccine and discusses the manufacture of antibodies by the intracellular synthesis of globulin under the influence of specific and nonspecific antigens. Alexander summarizes our knowledge of the process of desensitization in atopic disease and in contact dermatitis. The nonspecific approaches to the problem are also mentioned. Bigler reviews the reports in the literature on allergic and nonallergic reactions to toxoids and points out the lack of value in doing skin tests in an effort to anticipate them.

Protection of the Infant Against Diphtheria During the First Year of Life Following the Active Immunization of the Pregnant Mother. Liebling, J., and Schmitz, H. E.: J. Pediat. **23**: 430, 1943.

In a series of observations on a small group of pregnant women and their offspring, it was shown that active diphtheria immunization of mothers resulted in increased antitoxin titre of the offspring during the first year. This increase was usually sufficient to protect the infant from diphtheria during the first year of life, if the mother had originally been Schick-negative. It was less often sufficient if the mother had originally been Schick-positive. Unimmunized Schick-negative mothers gave birth to children who were also Schick-negative and remained so until over six months of age, whereas Schick-positive mothers gave birth to Schick-positive children.

The titres of diphtheria antitoxin in both mothers and children in this study were done by the intracutaneous method in rabbits. While the authors propose active immunization of certain mothers as a means of protecting their infants early in life, the data presented does not permit the conclusion that this can be done reliably.

Milk Intolerance, the Cause of a Nutritional Entity. McLendon, P. A., and Jaeger, D. S.: South. M. J. **36**: 571, 1943.

The authors have seen sixty-five instances of milk intolerance in the last five years in private practice. The degree of intolerance varied and did not always require complete elimination of milk. It was manifested in order of frequency by the following complaints: constipation, anorexia, abdominal distress, pallor, fatigue, irritability, respiratory symptoms, and frequency of urination. Eczema was not found in this group of patients. Ten per cent had a geographic tongue which responded to milk elimination by becoming smooth. Canker sores were more frequent than a geographic tongue. There was often a family history of allergy and not infrequently of milk intolerance in the mother. Bouts of diarrhea and of inexplained fever were also complained of, and tonsils were often enlarged and red. All these signs and symptoms improved with the complete or partial elimination of milk. Skin tests were not mentioned in the article.

Observations on Tetanus Immunization. Miller, J. J., and Hunter, J. B.: J. Pediat. **23**: 516, 1943.

In a comparison of two injections of alum-precipated tetanus toxoid with three injections, the author finds the latter a preferable routine pediatric procedure. Taking 0.1 unit of antitoxin per c.c. of serum as a presumably protective level, he finds that fifteen out of fifty-four children who had received two injections fell below this level 9 to 15 months after completion of the injections. Only four of forty-two children who had received three injections were correspondingly low after

such an interval. Though not quite statistically significant, the author considers the difference striking.

The three-injection group consisted of sixty-eight children who received 1 c.c. of combined diphtheria and tetanus alum-toxoid at a minimal interval of eight weeks and a third injection of 0.5 c.c. of alum-tetanus toxoid at a minimum of sixteen weeks later. In the two-injection group, ninety-three children received the first two, but not the third injection. The antitoxin titrations were done in mice and were reported as above or below the 0.1 and 1.0 unit levels.

The rapidity of response to a "recall" injection of fluid toxoid, as compared to alum-toxoid, was also studied. Fifteen of sixteen children reinjected with fluid toxoid and tested on the fourth or fifth day showed increases in titre. On the other hand, only thirteen of twenty-four children reinjected with alum-toxoid showed increases in titre at this time. From the sixth day on, all children in both groups showed increases in titre. This study of rapidity of "recall" response was made twelve to fifteen months after basic immunization. One c.c. of fluid toxoid was used or 0.5 c.c. of alum-toxoid. The author then favors three injections of alum-toxoid at three monthly intervals for basic immunization and the use of fluid toxoid when laceration occurs.

Concerning the Presence of Allergic Reactor Substances in the Tears of Tubercular Children. de Elizalde, P., Alonso, A. E., and Cerruti, G. C.: Bol. Acad. Nac. de med. de Buenos Aires, 168, June, 1943.

Elizalde had previously observed that when the tears of children with (tuberculous) phlyctenular conjunctivitis were injected into children with a positive tuberculin test, a reaction similar to the Mantoux test resulted. The tears of tuberculin-sensitive children who did not have phlyctenular conjunctivitis gave similar results, but tears from negative reactors did not.

Further investigation of this problem has confirmed these observations and has shown that only tears from tuberculin-positive children give a positive test. However, all tuberculin-positive cases do not react similarly with tears from tuberculin-positive cases (presumably because they do not have so high a degree of allergy as the conjunctivitis cases). In 168 tuberculin-positive children, 115 gave positive reactions to the tears from tuberculous cases while the remaining 53 were negative.

The authors conclude that a "reactor substance" is present in the tears; this behaves in the same manner as tuberculin of approximately 1 to 10,000 dilution.

Physiotheraputic Treatment of Asthma in Children. Bisquert, L., Bustamante, W., and Munoz, O.: Rev. chilena de pediat., 469, July, 1943.

This paper deals with the treatment of asthma by means of physical exercises and massage. The authors employ this approach in cases con-

sidered to be allergic as well as nonallergic, in both of which it has given good results. Treatment is discussed in detail under four headings; mechanical massage, manual massage, educative respiratory exercises, and corrective respiratory exercises. The authors state that in all patients vital capacity was improved and expiration facilitated. They state that physiotherapy can be begun even during an attack, and that after training, patients can get relief from an attack by light exercises. The exercises should be continued over a considerable period of time if improvement is to be maintained. The benefits of treatment are reflected in improved chest expansion, prevention of emphysema, improved musculature, and improved circulation.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Sinusitis in Children. Shea, J. J.: South. M. J. **35**: 74, 1942.

Shea emphasizes the importance of collaboration between the pediatrician and the rhinologist in the cases of children with sinusitis, since the therapy combines general hygiene, dietetic and constitutional measures with local therapy. He favors the Parkinson position for the instillation of a weak solution of ephedrine in young children, and direct suction or displacement and washing of the sinuses if the secretion is purulent or the patient is suffering from a persistent night cough or renal derangement. In cases of stubborn infection in which these measures fail and the economic status prohibits the child's being taken to a warm climate, he recommends dilation of the natural ostium under general anesthesia and draining of the sinus through an artificial window.

A Study of the Value of a Mixed Bacterial "Oral Cold Vaccine." Segel, M., Randall, M. G., Hecker, M.D., and Reid, M.: Am. J. M. Sc. **205**: 681, 1943.

A study of the value of a mixed bacterial oral cold vaccine was reported by Segal and his co-workers. The preparation was given by mouth to a group of 125 subjects. A control group of 128 persons was given capsules of similar appearance and containing the same ingredients without bacteria. The test period lasted through the winter months, from September 3, 1940, to March 30, 1941. Careful records were kept of the number and severity of the colds occurring in each group. No significant difference was noted between the group receiving the vaccine and the control group in either the number of colds occurring in this period, their severity, or the incidence of secondary bacterial complications.

Book Review

Allergy. E. Urbach, and C. M. Gottlieb, New York, 1943, Grune & Stratton, 1073 pp., illustrated.

THIS is probably the most pretentious book on allergy ever published. It is well organized as to context, beautifully illustrated, and contains some 2,300 references to literature on the subject.

The reviewer is left with two separate impressions. One is the completeness with which the subject is treated. All phases of allergy are dealt with, even disorders only remotely connected with it, and the brief space allotted to these contrasts properly with the minuteness of detail in which the more important phases are considered.

In places, there seems unnecessary repetition, as for instance, the photographic demonstration that lichen urticatus may be caused by foods. Figs. 346, 347, and 348 show the same lesion due to beef, 352 and 355 to wheat, 354 to milk, 353 to spinach, and 351 to egg. Likewise, angioneurotic edema, urticaria, and other skin lesions are portrayed with much repetition and little variation, excepting in the caption of different etiologic agents. This stress on detail in places assumes exaggeration, as in the appendix, where a suggestion is given for the study of patients. This consumes 12 printed pages for each patient and seems wholly impracticable. However, these are minor criticisms.

Perhaps the place where the authors missed an opportunity, a difficult one to accomplish, to be sure, was in an effort to tie in this far-flung subject to a cohesive, readily understandable unity in which there is a place for all that they speak of. This is exactly what they tried to do, but their own nomenclature which has never been generally accepted, with its complicated definitions and diagrams, clouds the picture rather than brightens it. Likewise, other of the authors' theories which after many years have little acceptance are urged upon the reader. One deals with propeptan therapy. The many explanations of why it so frequently fails and all the precautions necessary to make it work eventually are scarcely in its favor.

The book contains a wealth of information and serves as an excellent work of reference.